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TREATMENT IN BOTULISM *

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Medical research during the past ten years has greatly advanced our knowledge of *Clostridium botulinum (Bacillus botulinus)* and of *botulism*. Recent occurences of *botulism* in man and domestic animals throughout the United States, and particularly in California, have drawn attention to and greatly stimulated research in all phases of this disease. Until recently these researches were conducted mainly by investigators connected with the national government and state institutions. The National Canners Association is spending large sums of money investigating food poisoning with the object of improving canning methods and preventing further outbreaks of botulism.

E. C. Dickson [1] has energetically attacked the problems connected with the subject of botulism. He has established the common occurrence of botulism in the United States, the fact that toxin is found in preserved fruits and vegetables, the occurrence of two types of toxin in this country, as in Europe, the relation between *C. botulinum* and "limberneck" in chickens and the symptom complex.

G. S. Burke [2] has established the common occurrence of the organism in nature and the extreme heat resistance and heat inhibition of the spores, thus accounting for the occurrence of the organism and its toxins in preserved foods. She has also designated the two types of *C. botulinus* found in this country as types A and B.[3]

Robert Graham [4] and his co-workers have made extensive investigations and have definitely established the relation between *C. botulinum* and forage poisoning.

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* From the Department of Bacteriology and Experimental Pathology, Stanford University.

1. Dickson, E. C.: Botulism, Monograph No. 8 of the Rockefeller Institute for Medical Research, and subsequent papers.

2. Burke, G. S.: The Occurrence of *B. botulinus* in Nature, J. Bacteriol. **4**:541 (Sept.) 1919; The Affect of Heat on the Spores of *B. botulinus*, J. A. M. A. **72**:88 (Jan. 11) 1919.

3. Burke, G. S.. Notes on *B. botulinus*, J. Bacteriol. **4**:555 (Sept. 5) 1919.

4. Graham, Robert: Studies in Forage Poisoning, Bulls. 207 and 208, Kentucky Agricul. Exper. Station, and subsequent papers.

A number of others have verified and extended the results of these workers, so that at the present time we have a fairly satisfactory knowledge of *C. botulinum* and the symptoms produced by its toxins in man and domestic animals.

While our knowledge has been developing along these lines, there has been little or no advance toward a satisfactory treatment in botulism. The Europeans had already shown that an antitoxin could be produced and would neutralize the toxin in "in vitro" and to a limited extent in "in vivo" experiments. Kemper [5] was able to show that if antitoxin was injected twenty-four hours after the injection of a forty-eight hour fatal dose of toxin, a number of the animals could be saved. And Dickson and Howitt [6] have verified these findings and shown that when rabbits are fed the toxin in amounts sufficient to cause death in forty-eight hours, the injection of a homologous antitoxin in twenty-four hours will save the animals. No one has, so far as I am aware, fed toxic cultures of *C. botulinum* and then shown that the animals could be saved by the use of an antitoxin after the symptoms appear. This is the condition met with in general practice, and until it is shown that men or animals can be saved from fed lethal doses of toxic cultures of *C. botulinum* by the injection of antitoxin at or about the time that the symptoms appear, we must not look forward with any great expectations to the use of antitoxin in the treatment of botulism.

An examination of the literature offers no encouragement in so far as nonspecific treatment is concerned. We find that physicians have used a wide range of substances in treating cases of botulism. None of these men affirm that the treatment used materially altered or checked the course of the disease.

In viewing the problems presented by our present knowledge of the subject it seemed to us that future research in the treatment of botulism should proceed along four definite lines: (1) to determine the exact nature of the action of the toxin in the body; (2) to determine whether the toxin is extensively produced in the animal body and if produced, to develop some means of preventing its production; (3) to determine the amount of protection to be expected from the use of antitoxin if given at or about the time the symptoms appear; (4) the development of some preliminary treatment which will delay or prevent any further absorption of the toxin pending the arrival of the physician or the antitoxin.

We have no exact knowledge of the nature of the action of the toxin in the body. The result of the action is very evident in loss of

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5. Kempner: Weitere Beiträge zur Lehre von der Fleischvergiftung. Das Antitoxin des Botulismus, Ztschr f. Hyg. u. Infectionskrank **26**:481, 1897.

6. Dickson and Howitt: Botulism. A Preliminary Report of a Study of the Antitoxins of *B. botulinus*, J. A. M. A. **74**:718 (March. 13) 1920.

muscular control, death usually resulting from respiratory failure. It has not been determined whether the action of the toxin is central or terminal. The solution of this problem may give us a starting point for the development of some treatment of value.

It is generally stated in the literature that botulism is caused by the ingestion of preformed toxins. Orr [7] has taken issue with this statement and presents the results of some experiments which suggest that some cases of botulism may be due to an infection. This is important to the physician as well as to the canners. It is obvious that if we are dealing with an infection, the treatment must differ from what it should be if we are dealing only with the ingestion of preformed toxins. This question of infection will be discussed in detail later.

The experience recorded in the use of antitoxin in practical therapy is largely discouraging. There are several reasons for the apparent failure of the antitoxin treatment in botulism, the principal ones being that in most cases a heterologous antitoxin was used, and in all cases the treatment was commenced late in the course of the disease, usually several days after the symptoms appeared. Further experimental work should be done to determine just how effective the antitoxin treatment will be in all stages and conditions of botulism.

Since antitoxin is obtained only after delay, if obtained at all, it is essential that the attempt be made to develop some effective non-specific treatment. Most of the experimental work recorded in this paper was done in an effort to develop a treatment of this type. It was planned to make an exhaustive study of this phase of the subject but unfavorable conditions forced a termination of the work and this preliminary report is presented with the hope of stimulating others to carry on these researches to a definite termination.

An examination of case reports shows that the different treatments used have been designed to stimulate the patient, to prevent further absorption of the toxin and to neutralize the toxin by the use of antitoxin. No one has made any serious attempt to show that the organism or its toxins can be destroyed in the digestive tract. The results obtained from the treatments used are very discouraging. No one ventures to assert that the treatments used have altered the death rate. Dickson [8] recommends emesis, lavage, purgation with magnesium sulphate or castor oil, irrigation of the colon, giving water by rectum or by hypodermoclysis, strychnin, pilocarpin to counteract diminished secretions, cardiac and other stimulants as needed. Frost [9] recommends

7. Orr: Abstr. Bacteriol. **4**:10 (Feb.) 1920.
8. Dickson: Monograph No. 8, Rockefeller Institute for Medical Research.
9. Frost: Am. Med., February, 1915, p. 85.

the use of ipecac to stimulate glandular secretions in the intestines to check absorption. He also recommends rectal feeding, heroin, calomel, epinephrin, peptonized milk and whisky. Others have resorted to the use of digitalis, camphor, atropin, sodium phosphate, intravenous injections of salt solution, Glauber's salt, Epsom salt, olive oil, strophanthin, pituitary extract, gelsemium, colon enemas, stomach pump for evacuation and feeding, feeding through duodenal tube, and warm blankets for making the patient more comfortable. In a few cases the patient reported some temporary relief. Pilocarpin gives temporary relief from the accumulation of tenacious mucus in the pharynx. Pneumonia is frequently a complicating cause of death and should always be guarded against.

INFECTION VERSUS PREFORMED TOXINS

The possibility of botulism resulting from the ingestion of toxin-free organisms is discussed here in considerable detail because of its importance to the canning industry, to the epidemiologist, its bearing on the treatment of botulism and because the available data are not conclusive.

After considerable experimental work, von Ermengem [10] concluded that *C. botulinum* does not produce its toxins in the animal body. He fed washed bacilli and also injected them subcutaneously and intravenously without producing symptoms of botulism. He recovered the organism from the spleen and liver but could not demonstrate its presence in sections.

Thom, Edmondson and Giltner [11] attempted to determine whether *C. botulinum* spores freed from toxin by heating and by washing with salt solutions would produce toxin within the animal body. They found that if cultures containing spores were freed of toxin by heating to 80 C. for ten minutes and then were fed to or injected into animals no symptoms developed. If the organisms were washed seven times and injected into guinea-pigs or rabbits, the animals died, but if the cells were washed fourteen times the animals lived. In the heated cultures, the bacilli and their toxins were destroyed, leaving only the spores. In the washed cultures, the cells and spores remained, only the toxin being removed. The results obtained from washing the organisms fourteen times seem to indicate that the difference in results between heating and washing seven times is not due to the presence of more cells or to the presence of bacilli as well as spores and the produc-

10. Von Ermengem: Contributions à l'etude des intoxications alimentaires, Arch. pharmacodyn. **3**:213 1897.

11. Thom, Edmondson and Giltner: J. A. M. A. **73**:907 (Sept. 20) 1919.

tion of toxin in the body, but to the presence of preformed toxins which were not washed away. The organisms were recovered from the feces of the animals which were fed spores (freed from toxin either by heat or by washing), and from the liver and spleen of animals injected with cultures. These authors conclude that "colonization of the bacilli in the body has not been proved thus far, but the foregoing isolations from feces prove that the organism goes through the guinea-pig's body in from twenty-four to forty-eight hours with undiminished virulence."

Armstrong, Story and Scott [12] repeated with some modifications the experiments of Thom, Edmondson and Giltner. They injected subcutaneously in guinea-pigs 300,000,000 bacilli, previously heated to 80 C. for thirty minutes. No symptoms developed. The bacilli undoubtedly were killed by the heat, and they do not estimate the number of spores present. Cultures following the heating indicated the presence of viable organisms. Guinea-pigs injected subcutaneously with 300,000,000 bacilli, previously washed twelve and fourteen times, respectively, died. A guinea-pig injected subcutaneously with 120,000,000 organisms which had been washed on a Berkefeld filter by passing 800 c.c. of saline solution through the filter died in four days. Guinea-pigs receiving 12,000,000 similar organisms remained well. A guinea-pig force fed 1,200,000,000 washed organisms died in seventy hours, while another animal given the organisms on grass and meal showed no symptoms. The authors apparently favor the view that it is difficult to wash the toxin from the bacilli and that the death of the guinea-pigs in their experiments was due to this failure rather than that the toxin was produced in the animal bodies. It seems to us that a third explanation is possible, i. e., that there is some intracellular toxin and this is liberated on the death and lysis of the bacilli. This may explain the results obtained in the experiments of Armstrong, Story and Scott, in which a guinea-pig receiving 120,000,000 or more washed bacilli died, while a guinea-pig receiving 12,000,000 similar organisms lived. However, it does not explain the results obtained by Thom, Edmondson and Giltner in which it was shown that a guinea-pig injected with bacilli washed seven times died, while a guinea-pig injected with the same number of bacilli washed fourteen times lived, unless we assume that continued washing extracts the toxin from the interior of the cells.

Orr [13] has recently recorded some experiments which differ from those already described. All the details of Orr's work are not yet available so that we cannot carefully compare his experiments with the work of others. Orr found that guinea-pigs receiving large numbers of

12. Armstrong, Story and Scott: Pub. Health Rep. **74**:2894 (Dec. 19) 1919.
13. Orr: Abstr. Bacteriol. **4**:10 (Feb.) 1920.

toxin free spores (heated to 80 C. for thirty minutes) either per os or subcutaneously, usually died in from two to four days. Control pigs receiving antitoxin lived. The organisms were recovered from the spleen and liver in many of the animals, and in one case botulinus toxin was demonstrated in the brain tissue by mouse inoculation. Orr concludes that some cases of botulism may be due to a true infection.

Orr's results differ from those of other workers and suggest that *C. botulinum* may develop and produce its toxins in the animal body. Whether it ever happens that toxin-free organisms are ingested in sufficient numbers to cause botulism is of more interest to the canners and epidemiologists than to the physician. What is of particular interest to the medical profession from the standpoint of treatment is whether the toxin is being produced in the patient after the symptoms appear. The first case requires that the organisms grow and produce toxin in a normal digestive tract; the second, that the organisms grow and produce toxin after peristalsis has been reduced or has ceased. If the first occurs, the second naturally follows, but not the reverse. The production of toxin in the human body, if it occurs at all, may occur only after the ingestion of preformed toxin. Experiments were begun to determine this point, but were not carried far enough to warrant reporting.

If botulism ever occurs in human beings following the ingestion of toxin-free bacilli or spores we should find evidence of it. (1) There should be recorded outbreaks of botulism without a history of spoiled food and (2) without a history of preserved food. (3) It should be possible to demonstrate experimentally an infection following the ingestion of toxin-free organisms. (4) There should be more cases of botulism, unless an extremely large number of organisms are necessary for the development of an infection. (5) Outbreaks of botulism should follow the eating of thoroughly cooked spoiled preserved foods.

1. THERE SHOULD BE RECORDED OUTBREAKS OF BOTULISM WITHOUT A HISTORY OF SPOILED FOOD

We cannot say that all outbreaks of botulism have been due to spoiled food. Nor can we say that there have been outbreaks of botulism without a history of spoiled food. The records of the early outbreaks are incomplete. In all recent, thoroughly investigated outbreaks it has been stated by some of those involved in each outbreak that the food under suspicion tasted a little "off"; others have stated that they noticed nothing peculiar about the food, and, in fact, liked it.

This criterion is of little value in helping us to reach a decision because of the fact that spoiled foods are not readily separated from

unspoiled foods, and that people are careless about discarding food that is slightly suspicious. The standards by which spoilage in food is judged differ with different people, and food containing a naturally strong or peculiar odor may be in the early stages of botulinus spoilage and contain toxin sufficiently strong to cause disease without the taste, smell or appearance being sufficiently altered to attract the attention of the average individual. Also when mild flavored, slightly decomposed food containing toxin is mixed with other foods the detection of any unusual condition of the food is difficult. Such foods would be classed as unspoiled by some individuals. Some scientific observers believe that botulinus spoilage in preserved foods can always be detected by a careful examination, others are doubtful, The subject of botulism has received such publicity that we may expect to see a reduction in the number of outbreaks in families where the housewife oversees the cooking, but in many institutions and public eating houses the ignorant cook still rules. For this reason, the evidence given as to the condition of the suspected food will in some cases be inconclusive and of little value in determining whether there are ever any outbreaks of botulism without a history of spoiled food.

2. THERE SHOULD BE RECORDED OUTBREAKS OF BOTULISM WITHOUT A HISTORY OF PRESERVED FOOD

It has been shown that *C. botulinum* occurs in nature on fresh fruits and vegetables. It follows that many of us ingest the organisms without ill effects. If the ingestion of small numbers of toxin-free spores causes an infection, we should have cases of botulism without a history of preserved food having been eaten a short time before the onset of the symptoms. The epidemiologic data concerning most of the outbreaks of botulism are not sufficiently detailed to prove without question that a certain food caused the outbreak. But the fragmentary evidence that we have indicates that all outbreaks of botulism have been preceded by the eating of preserved food. It has not been shown in the early outbreaks of botulism that these preserved foods contained the toxin or the organism of *C. botulinum*. However, in all recent thoroughly investigated outbreaks it has been shown that the preserved foods eaten, if any remained for investigation, contained *C. botulinum* or its toxin. Therefore, we feel justified in believeing that botulism in man does not follow the ingestion of toxin-free spores, particularly in small numbers. We have no evidence that large numbers of toxin-free spores are ever ingested, except in cooked spoiled food. And the destruction of the toxin in spoiled foods by thorough boiling for a few minutes does not destroy the spores but does appear to prevent botulism.

3. IT SHOULD BE POSSIBLE TO DEMONSTRATE EXPERIMENTALLY AN INFECTION FOLLOWING THE INGESTION OF TOXIN-FREE ORGANISMS

We have already cited the results obtained by von Ermengem, Thom, Edmondson and Giltner, and Armstrong, Story and Scott, in which infections did not follow the feeding and injecting of toxin-free organisms, and of Orr, who was able to demonstrate the presence of toxin in the animal body following the feeding of toxin-free spores. The conflicting results obtained by these workers have not been explained, and we must await repeated experiments for knowledge of the determining factors. Orr's results suggest that an infection may sometimes follow the ingestion of large numbers of toxin-free spores.

THERE SHOULD BE MORE CASES OF BOTULISM UNLESS AN EXTREMELY LARGE NUMBER OF ORGANISMS ARE NECESSARY FOR THE DEVELOPMENT OF AN INFECTION

As has already been stated, the organisms are fairly common in nature, and many of us ingest them without the development of an infection. That there are not more cases of botulism indicates that a few toxin-free organisms will not start an infection in a normal individual. The experimental evidence shows that an infection following the ingestion or injection of toxin-free spores does not occur unless very large doses are given. We cannot conceive of any condition under which a very large number of toxin-producing organisms of *C. botulinum* would be ingested, except in the eating of heated preserved foods. Orr has reported strains of *C. botulinum* as having lost the power of toxin production. Such strains growing in preserved foods might afford an opportunity for the ingestion of toxin-free organisms. Since the virulence of the organism depends partly on toxin production, it is a question whether such strains, even if taken in large numbers, would regain the power of toxin production and cause an infection.

The statistical and experimental evidence indicates that botulism does not follow the ingestion of small numbers of toxin-free organisms. Whether toxin-free organisms ever occur in preserved foods, heated or unheated, in sufficiently large numbers to cause an infection in man is doubtful.

THERE SHOULD BE CASES OF BOTULISM FOLLOWING THE EATING OF THOROUGHLY COOKED SPOILED PRESERVED FOODS

No cases of botulism are recorded in this country as following the eating of thoroughly cooked food. We assume that much spoiled food has been cooked and eaten. Outbreaks are reported in which the eating of uncooked spoiled food caused botulism and the eating of portions

of the same food after cooking caused no symptoms. This is not entirely conclusive since occasionally a person eating the uncooked food also escapes illness. At least seven individuals have been reported as having eaten of food causing botulism in others without becoming ill.

Since there are no recorded outbreaks of botulism in this country following the eating of cooked spoiled food, and since the spores are highly resistant to heat, we believe it reasonable to assume that large numbers of spores have been eaten without causing symptoms of botulism.

It is to be expected, however, that cases of botulism will occasionally occur from the eating of insufficiently cooked or heated spoiled food. A little warming will not destroy all the toxin. Spoiled food containing considerable gas appears to be boiling at temperatures of from 70 to 80 C. Bubbles may rise to the surface for at least five minutes before the true boiling point is reached. The statement is found in the literature that boiling spoiled food for five minutes makes it safe to eat. Thom, Edmondson and Giltner reported that at a temperature of 75 C. no appreciable time is required for the destruction of the toxin in a filtrate. Orr records destruction of the toxin in two minutes at 80 C. Others have reported similar findings. Boiling ordinary canned fruits and vegetables for five minutes should raise the temperature in the fruits or vegetables up to or above 75 C. and cause the destruction of all the toxin present, unless the toxin in the fruit tissues and juices is more resistant to heat than toxin in filtrates. In foods in which there is so much gas present that boiling appears to begin at 75 C., an exposure to this temperature for five minutes may not destroy all the toxin in the interior of the food, and botulism may result from the eating of such cooked food and be caused by the undestroyed toxin.

Experiment to determine the effect of heat on the disease producing power of the juice from a can of spoiled beans containing C. botulinum and its toxin.—The following experiments throw some light on the questions here involved and they simulate as nearly as possible conditions found in home cooking. The beans used were canned six months previously and contained a strong Type A toxin. The beans were badly spoiled and contained gas. One half pint of the beans with the juice was placed in a large beaker and brought to a boil. At intervals some of the juice was withdrawn and injected subcutaneously into guinea-pigs. The results obtained (Table 1) indicate that:

1. Spoiled foods containing gas may appear to be boiling for several minutes before the true boiling point is reached.

2. The destruction of the toxin in the bean juice may require considerable more exposure to heat than is recorded for toxin in filtrates.

3. Under the conditions of this experiment the disease-producing power of the bean juice was not wholly destroyed after exposure for nine minutes to temperatures changing from 70 C. to 100 C. or after exposure to boiling for four minutes.

4. The disease producing power of a can of spoiled beans containing *C. botulinum* and its toxin may be destroyed by a temperature that does not destroy the spores of *C. botulinum*.

5. Spoiled canned foods may appear to have boiled seven minutes and still be unsafe to eat.

TABLE 1.—Effect of Heat on the Disease Producing Power of Juice from Spoiled Beans Containing C. Botulinum and Its Toxin

Time Minutes	Temperature and Appearance of Beans	Guinea-Pig	Weight, Gm.	Amount Injected, C.c.	Results
	Unheated	1	250	1	Dead 18 hours
	Unheated	2	250	0.01	Dead 18 hours
0	Burner lighted				
4	70 C. bubbles beginning to rise				
6	82 C. active bubbling, resembling boiling				
7	92 C. active bubbling, resembling boiling	3	250	1	Dead 96 hours
8	98 C. large bubbles				
9	100 C. true boiling	4	250	1	Dead 96 hours
13	100 C. true boiling	5	250	1	Dead 17 days
19	100 C. true boiling	6	250	1	Lived

In this experiment no effort was made to determine whether the animals died from the effects of the toxin formed in the can of beans or in the animal body. A filtrate of the heated juice was not tested for toxin and the presence of spores was not determined. However, one fact of importance is evident. The disease producing power of a can of spoiled beans may be destroyed by a temperature that does not destroy the spores of *C. botulinum*. Exposure of the spores to a temperature of 100 C. for ten minutes does not prevent their development and toxin production in culture mediums. If the spores ever cause an infection, heat may affect their virulence for the animal body. This experiment cannot serve as the basis for any definite conclusions as regards the infection theory because of the three unknown and uncontrolled factors: (1) the effect of heat on the toxin in bean juice; (2) the effect of heat on the vegetative forms in bean juice; (3) the presence of spores and the effect of heat on the virulence of the spores of *C. botulinum*. The results indicate, however, that we may expect to have outbreaks of botulism following the eating of poorly cooked spoiled food.

The results of this experiment indicate that spoiled food to be safe to eat must be boiled for at least fifteen minutes. And if the spores of *C. botulinum* are found to cause an infection in man, a much greater exposure to heat may be required. Boiling for four hours does not destroy all the spores of *C. botulinum*.

Experiment to determine the effect of boiling on the disease producing power of the juice from a can of spoiled beans containing C. botulinum and its toxin when oil stratified.—About 100 c.c. of the beans and juice used in the preceding experiment were placed in a beaker, oil stratified, and exposed to heat at 100 C. The results obtained (Table 2) were similar to those of the preceding experiment, except that the disease producing power of the bean juice resisted the effects of the heat for a longer period of time. Guinea-pigs receiving 1 c.c. of the bean juice, exposed to 100 C. for ten minutes, died.

TABLE 2.—EFFECT OF TEMPERATURE OF 100 C. ON THE DISEASE PRODUCING POWER OF JUICE FROM SPOILED BEANS CONTAINING C. BOTULINUM AND ITS TOXIN WHEN OIL STRATIFIED

Time, Minutes	Temperature	Amount of Juice Injected, C.c.	Guinea-Pig	Weight, Gm.	Result
	Unheated	1	1	250	Dead, 18 hours
	Unheated	0.01	2	250	Dead, 18 hours
0	Burner lighted				
6½	100 C.				
11½	100 C.	1	3	250	Dead, 96 hours
16½	100 C.	1	4	250	Dead, 96 hours
21½	100 C.	1	5	250	Lived
26½	100 C.	1	6	250	Lived

Experiment to determine the effect of a temperature of 80 C. on the disease producing power of a can of spoiled beans, containing C. botulinum and its toxin, when oil stratified in a test tube and placed in a water bath.—About 15 c.c. of the beans and juice used in the preceding experiments were placed in a test tube and oil stratified. This test tube was then placed in a water bath and kept at 80 C. No record was taken of the temperature in the test tube. Some of the bean juice

TABLE 3.—EFFECT OF TEMPERATURE OF 80 C. ON THE DISEASE PRODUCING POWER OF JUICE FROM SPOILED BEANS CONTAINING C. BOTULINUM AND ITS TOXINS WHEN OIL STRATIFIED IN A TEST TUBE AND PLACED IN A WATER BATH

Time, Minutes	Temperature	Amount of Juice Injected, C.c.	Guinea-Pig	Weight, Gm.	Result
	Unheated	1	1	250	Dead, 18 hours
	Unheated	0.01	2	250	Dead, 18 hours
0	Test tube containing beans placed in water bath				
11	80 C.	1	3	250	Dead, 72 hours
30	80 C.	1	4	250	Dead, 72 hours
61	80 C.	1	5	250	Dead, 72 hours

was taken from the test tube at intervals and injected into guinea-pigs. The results obtained (Table 3) indicate that under the conditions of this test, which largely resembles the conditions surrounding beans in the middle of a kettle placed on the stove to warm, the disease producing power of the bean juice was not destroyed after an exposure to a temperature of 80 C. for one hour. This suggests that the casual warming of spoiled foods to a temperature of 80 C., even over an

extended period of time may not make them safe to eat. Since such foods may appear to be boiling, it is evident that we may expect to have cases of botulism following the eating of so-called boiled foods. The epidemiologist must bear these facts in mind in investigating outbreaks of botulism.

INFECTION FOLLOWING THE INGESTION OF THE TOXIN AND THE ORGANISMS

While it is of great importance to the epidemiologist to know whether botulism ever follows the ingestion of toxin-free organisms, it is of equal importance to the physician to know whether an infection ever occurs following the ingestion of the toxin and the organisms. If botulism ever occurs following the ingestion of toxin-free spores, we may be justified in assuming that an infection may occur following the ingestion of both the toxin and the spores, particularly after the symptoms appear. In the latter case, conditions for the development of *C. botulinum* are presumably more favorable than in the normal digestive tract.

If an infection ever occurs this may account for relapses that sometimes follow an improvement in the condition of the patient. It sometimes happens that a patient shows considerable improvement and then suffers a relapse and dies. This may be accounted for on the basis of a required incubation period, the first symptoms being due to the ingested toxin and the relapse due to toxins produced in the body. Stiles,[14] in recording his own case states that he had a serious relapse after partially recovering from the first attack. Others have reported similar experiences.

If an infection occurs, i. e., production of toxin in the digestive tract or elsewhere in the animal body, following the ingestion of the toxin and the organisms of *C. botulinum* the following postulates should hold true.

1. There should be, within certain limits, no relation between the amount of infected food eaten and the severity of the symptoms. If infection does not occur then there should be a definite relation between the amount of food eaten and the severity of the symptoms. (Individual variations in resistance, effects of other foods eaten and the even distribution of the toxin in the food are modifying factors that must be taken into consideration.)

Armstrong, Story and Scott,[15] in investigating the Canton, Ohio, outbreak found a "remarkable correspondence between the amount

14. Stiles: J. A. M. A. **61**:2301 (Dec. 27) 1913.
15. Armstrong, Story and Scott: Pub. Health Rep. **34**:2877 (Dec.) 1919.

eaten and the severity of the illness." Those eating less of the poisonous food obtained less toxin and also a smaller number of organisms but "had the bacilli swallowed with the olives been capable of growing and producing toxin in the alimentary tract it seems that some of the people who ate small amounts but were little affected would have developed serious symptoms." They estimated that one olive contained several million bacilli and conclude that "a bite of olive containing this number of viable organisms, if capable of multiplying and forming toxin in the alimentary tract, would have caused serious infections." However, this does not show that an infection may not occur following the ingestion of large numbers of organisms and after paralysis has set in.

2. It should be possible to demonstrate the infection experimentally since the M. L. D. (minimum lethal dose) of the filtrate should be less than the M. L. D. of the culture.

Any difference in toxicity between filtrate and culture should be due to the organisms present in the culture unless the process of filtering eliminates some of the toxin as well as the organisms. Emerson and Collins[16] report that olive juice from spoiled olives "filtered through a Berkefeld filter was found to be slightly less toxic than the unfiltered juice." We await further experimental evidence of a similar nature.

3. If infection occurs in the body outside of the digestive tract it should be possible to detect the organisms in sectioned material. *C. botulinum* has been recovered at necropsy from the liver and spleen of both human and laboratory animals dead of botulism. If the organisms are able to multiply and start an infection in the spleen and other organs it should be possible to demonstrate their presence in sectioned material. All attempts to demonstrate the organism in microscopic sections of organs of animals dead of botulism have been unsuccessful.

CONCLUSION

The major evidence as we have presented it here favors the view that botulism in man very rarely, if ever, occurs following the ingestion of toxin-free organisms. The available evidence is too inconclusive to form the basis for any definite conclusions. Many of the facts presented can be explained in more than one way. Our own belief is that infection in human beings following the ingestion of toxin-free organisms never occurs. We are inclined to believe that the organism does produce toxin in the alimentary tract following the ingestion of preformed toxins and after paralysis has set in. Treatment

16. Emerson and Collins: J. Lab. & Clin. Med. **5**:559 (June) 1920.

of the digestive tract should be designed to neutralize and wash out the toxin and inhibit or destroy the organisms.[17]

IMMUNE SERUM TREATMENT

Workers in Europe and in this country have shown that repeated injections of sublethal doses of *C. botulinum* toxin in various animals will stimulate the production of specific antitoxins. Experiments have shown that the antitoxin will neutralize the toxin in "in vitro" experiments and in "in vivo" if the antitoxin is injected before the toxin, or after the toxin if the injection is made before the system is fatally damaged. Since there are at least two immunologically distinct types of *C. botulinum,* it is necessary to use a polyvalent immune serum unless the type of toxin is known.

The extent to which antitoxin is effective in preventing death when injected some time after the toxin has been taken into the body has not been established definitely. Kempner [20] has shown that if antitoxin is injected twenty-four hours after a forty-eight hour fatal dose of

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17. After the present article was sent to press our attention was called to an article by Edmondson, Giltner and Thom (The Possible Pathogenicity of Bacillus Botulinus, Arch. Int. Med. **26**:357 [Sept.] 1920), in which they discuss experiments the results of which agree with those of Orr. In referring to their experiments they state that, "They show that occasionally guinea-pigs will develop the specific disease and die when fed or injected with large doses of the spores freed from toxin in routine manner," i. e., by washing or heat or both. The authors contemplate experiments to determine whether the toxin causing the disease is present in the spores or bacilli when ingested or injected and protected from heat by the spore wall and released upon dissolution of the spore wall or is actually produced in the body after the spores germinate. One of the strains used caused death more consistently than the other. The feeding or injection of large numbers of organisms of the most virulent strain was not always fatal. One of the body defenses against anaerobe infection consists of the amount of oxygen in blood and tissue fluids. The injection of toxin free spores either subcutaneously or intravenously, may lead to a local lowering of the oxygen tension and necrosis making conditions favorable for the development of anaerobes. What factor this plays in experimental botulism remains to be determined. C. botulinum has not been recorded from war wounds. The experimental data suggests that it may occasionally occur in wounds and thus account for the failure of the patient to respond to tetanus and other common antitoxin treatment. The paper of Bullock and Cramer [18] suggests that the toxin free spores of tetanus are no more infectious than those of C. botulinum. The main problem from the standpoint of treatment is to determine whether there are outbreaks of botulism in man following the ingestion of toxin free spores and if such do occur whether the symptoms are typical or atypical as has been suggested by Shippen [19] and therefore leading to a wrong diagnosis.

18. Bullock and Cramer: A New Factor in the Mechanism of Bacterial Infection, Proc. Roy. Soc. London, Series B **90**:513, 1920.

19. Shippen: Arch. Int. Med. **23**:346 (March) 1919.

20. Kempner: Weiterer Beiträg zur Lehre von der Fleischvergiftung. Das Antitoxin des Botulismus, Ztschr. f. Hyg. u. Infektionskrankh. **26**:481, 1897.

toxin many of the animals will live. Dickson and Howitt [6] verified Kempner's findings to the extent of showing that if the antitoxin is injected subcutaneously within twenty-four hours after a forty-eight hour fatal dose of toxin has been ingested the animals will live. This means that when small doses of toxin are fed, twenty-four hours is not sufficient time for the toxin to be absorbed and cause fatal injury to the animal. Antitoxin must be used before the nervous system has been injured fatally. The time required for this depends upon the amount of toxin ingested or injected. If large amounts of toxin are used an animal may be injured fatally by the time the first symptoms appear.

The problem the practitioner has to face during an outbreak is to save the patients showing symptoms and also those who have eaten the poisonous food but have not yet shown symptoms. No one has, so far as we are aware, shown experimentally that an animal can be saved from lethal doses of toxin by the injection of antitoxin after the symptoms appear. And no one has attempted to show how many hours before the symptoms appear the injection of antitoxin will protect. The experiments of Kempner and of Dickson show that an animal can be saved from a forty-eight hour fatal dose of toxin by the injection of antitoxin twenty-four hours before death would occur if the antitoxin was not injected. They do not indicate how many hours this would be before the symptoms appeared. Dickson injected the antitoxin subcutaneously. It might have been possible to protect his animals by later injections if these had been made intravenously.

The available statistical data of the various outbreaks in this country show a death rate of 90 per cent. among those first showing symptoms, and a death rate of 60 per cent. among those last showing symptoms. Frequently, two or three days will elapse between the appearance of symptoms in the first patient and the last patient to come down in an outbreak of botulism. Sixty per cent. of the latter die. The experimental evidence gives us reason to believe that some of these victims could have been saved by the injection of antitoxin if the injections had been begun as soon as the first patient showed symptoms.

The following experiments were designed to determine the extent of the protection afforded by antitoxin if injected after the symptoms appear. In order to approach the conditions found in general practice toxic cultures instead of toxic filtrates were used.

Experiment to determine whether rabbits can be protected from lethal doses of toxic cultures of C. botulinum by the injection of antitoxin as soon as the symptoms appear.—Each rabbit was force fed 6 c.c. of a ten day meat culture of *C. botulinum* Type B. Antitoxin was injected both subcutaneously and intravenously seventeen hours later.

At this time two of the rabbits were dead, one was practically dead and three showed slight symptoms of prostration. Two of the rabbits receiving antitoxin lived. Since these rabbits received about 2 minimum lethal doses of toxin and were showing the first symptoms of botulism, there is no question that they would have died without the injections of antitoxin. The results obtained (Table 4) indicate that some rabbits can be saved from the forced feeding of a lethal amount of a toxic culture of *C. botulinum* by the injections of antitoxin as soon as the symptoms appear. It is probable that a larger percentage of rabbits can be saved by the injection of antitoxin after the symptoms appear if a smaller amount of toxin is fed.

TABLE 4.—Results of an Experiment to Determine Whether Rabbits Can Be Saved from Lethal Doses of Toxic Cultures of C. Botulinum When Force Fed by Injection of Antitoxin as Soon as Symptoms Appear

Rabbit	Weight, Gm.	Amount of Culture	Interval Before Injection of Antitoxin	Results
1	1,750	6 c.c. per os	.....	Dead, 16 hours
2	2,700	6 c.c. per os	.....	Dead, 16 hours
3	2,850	6 c.c. per os	.....	Dead, 17 hours
4	1,925	6 c.c. per os	17 hours	Lived
5	2,115	6 c.c. per os	17 hours	Lived
6	2,750	6 c.c. per os	17 hours	Dead, 23 hours

The experiment was repeated with the exception that the injection of the antitoxin was delayed until the symptoms were more advanced.

Experiment to determine whether rabbits can be saved from lethal doses of toxic cultures of C. botulinum by the injection of antitoxin after the symptoms are well advanced.—Each rabbit was force fed 6 c.c. of the meat culture used in the preceding experiment. The injections of antitoxin were begun twenty-one hours after the feeding of the toxic cultures and were made subcutaneously and intravenously. At this time three of the rabbits were dead and the three receiving antitoxin were prostrated. All the rabbits receiving antitoxin died. One of these lived for sixty hours, but it cannot be certain that this was due to the action of the antitoxin, as rabbits show considerable variation in their resistance to the toxin when force fed. The results obtained (Table 5) indicate that rabbits cannot be saved from 2 M. L. D., force fed, of a toxic culture of *C. botulinum* by the injection of antitoxin after the symptoms are well advanced and the rabbits show evident signs of prostration.

Botulinus antitoxin has been used in a number of outbreaks of botulism with inconclusive results. Dickson [21] was the first in this country to use antitoxin as a therapeutic agent in cases of botulism.

21. Dickson: Arch. Int. Med. **22**:483 (Oct.) 1918.

He used a Type A and B antitoxin and both patients recovered. The antitoxin was not injected until five days after the symptoms appeared, and he doubts whether it affected the course of the disease.

McCaskey [22] injected antitoxin in treating three patients in the Decatur outbreak and believed it to be the determining factor in the recovery of two of the patients. The third patient was almost dead at the time the antitoxin was administered. The antitoxin was not given until several days after the symptoms appeared.

Ransom [23] reports the use of antitoxin in the Clinton prison outbreak with beneficial results though given late in the course of the disease.

Randell,[24] Jennings, Haass and Jennings,[25] Armstrong, Story and Scott, and Sisco [26] report the use of antitoxin in treating patients suffering with botulism. No improvement in the condition of the patients was attributed to the use of antitoxin.

TABLE 5.—Results of an Experiment to Determine Whether Rabbits Can Be Saved from Lethal Doses of Toxic Cultures of C. Botulinum When Force Fed by Injection of Antitoxin After Symptoms Are Well Advanced

Rabbit	Weight	Amount of Culture	Interval Before Injection of Antitoxin	Results
1	1,750	6 c.c. per os	.....	Dead, 21 hours
2	1,950	6 c.c. per os	.....	Dead, 18 hours
3	2,100	6 c.c. per os	.....	Dead, 12 hours
4	2,000	6 c.c. per os	21 hours	Dead, 24 hours
5	1,900	6 c.c. per os	21 hours	Dead, 60 hours
6	2,100	6 c.c. per os	21 hours	Dead, 36 hours

In all cases in which antitoxin has been used in the treatment of botulism, the antitoxin has been given late in the course of the disease, sometimes in small amounts, or was of the heterologous type. Under such conditions we could not expect to get encouraging results.

Experimental work has shown that antitoxin to be effective must be given in excess before or very soon after the symptoms appear. Since a rapid determination of the type of organism producing the toxin is not possible, a polyvalent serum should be used. And since there is a possibility of *C. botulinum* producing its toxin in the body, the serum should be bacteriolytic or bactericidal as well as antitoxic. The serum should be injected intravenously. We have reason to hope that if antitoxin becomes generally available and is given to all those partaking of the suspected food as soon as the first patient shows symptoms, the death rate will be reduced materially.

22. McCaskey: Am. J. M. Sc. **158**:57 (July) 1919.
23. Ransom: Personal communication.
24. Randell: J. A. M. A. **75**:33 (July 3) 1920.
25. Jennings, Haass and Jennings: J. A. M. A. **74**:77 (Jan. 10) 1920.
26. Sisco: J. A. M. A. **74**:516 (Feb. 27) 1920.

EFFECT OF FOODS ON THE TOXIN AND DEATH RATE

A review of available literature brought out certain facts which suggested to us that the foods in the stomach may have an influence on the appeaarance of the symptoms and the death rate.

The death rate in Europe is from 25 to 30 per cent. less than the death rate in the United States. This difference in the death rate may be due to a number of factors. The principal ones are the following:

1. The outbreaks in Europe are mainly due to toxin formed in foods such as meats, sausage and cheese, which are usually not preserved in liquids. The outbreaks in the United States have usually been due to toxins formed in foods preserved in liquids, such as fruits and vegetables. It is possible that the organism produces a stronger toxin in the latter foods; or that the liquid facilitates absorption.

2. Different habits in the heating and cooking of foods may reduce the death rate. Heat destroys the toxin.

3. The outbreaks in Europe may be due to a different type of *C. botulinum*, or to a prevalence of Type B, which usually produces a weaker toxin than Type A. The majority of the outbreaks in the United States have been produced by the toxin of Type A.

4. The Europeans use more oils and alcoholic drinks with meals. These may affect the rate of absorption or the strength of the toxin.

5. Botulism is not so well known as a specific disease in this country, and it is possible that only the fatal outbreaks have been recognized and reported.

The following facts have a bearing on the question concerning the effects on the toxin of food in the stomach. Occasionally, a person eating the toxic food escapes illness. The appearance of the symptoms in persons eating the same amount of the toxic food varies in time and severity. Variations in the appearance of the symptoms and the mortality may be due to the toxin not being evenly distributed through the food, to individual variation in resistance and to the effect of other foods taken into the stomach at the same time. Armstrong, Story and Scott [15] report that in the Canton, Ohio, outbreak two of those eating heavily of the toxic food escaped with slight symptoms and attribute this to the whisky taken with the meal. They were able to demonstrate that alcohol neutralizes the toxin when the two are mixed in a test tube. In the Boise, Idaho, outbreak one of those eating heavily of the toxic food escaped illness. Van Ermengem states that the toxin is precipitated by alcohol, tannin and neutral salts, and that 20 per cent. normal soda destroys it in a short time. Brieger and Kempner [27] state that the toxin in dried form is susceptible to alcohol,

27. Brieger and Kempner: Beitrag zur Lehre von der Fleischvergiftung, Deutsch. med. Wchnschr. **23**:521, 1897.

ether and oxidizing agents. Forsman [28] reports that large doses placed in the large intestine of the rabbit produce no symptoms. The M. L. D. "per os" for rabbits is at least 300 times the subcutaneous M. L. D. These facts led us to investigate the effect of the stomach contents and various foods on the toxin of *C. botulinum*. We did not determine the effect of the contents of the intestines on the toxin or the potency of the toxin when introduced into the intestines.

Experiment to determine the neutralizing action of the stomach contents of a normal rabbit on the toxin of C. botulinum.—The contents of a full rabbit stomach was thoroughly dried in the incubator, then ground up in a mortar, mixed with an equal volume of diluted toxin and incubated two hours. The toxin used as a control was incubated at the same time. The toxin-stomach contents mixture was then centrifuged and the supernatant fluid injected subcutaneously into guinea-pigs. The results obtained (Table 6) indicate that the stomach contents of the rabbit do not neutralize or precipitate the toxin of *C. botulinum*.

TABLE 6.—Results of Neutralizing Action of Stomach Contents of Normal Rabbit on Toxin of C. Botulinum

Guinea-Pig	Amount Toxin	Results
Control 1	2 M. L. D.	Dead, 20 hours
Control 2	2 M. L. D., centrifuged toxin	Dead, 29 hours
Control 3	2 M. L. D., centrifuged toxin	Dead, 29 hours
4	2 M. L. D., toxin exposed to stomach contents	Dead, 29 hours
5	2 M. L. D., toxin exposed to stomach contents	Dead, 29 hours

The following experiment was designed to determine the comparative rates of absorption of the toxin in the full stomachs and starved stomachs of rabbits. Although the contents of a full rabbit stomach did not neutralize the toxin it was thought that it might affect the appearance of the symptoms and the death rate by mechanically slowing down the rate of absorption.

Experiment to determine the effect of starving and the subsequent empty stomach on the rate of absorption of the toxin in the rabbit.—Two rabbits were given water but no food for forty-eight hours. They were then given a small nibble of grass and force fed 4 c.c. of a toxic filtrate of *C. botulinum* Type B. The grass was fed to stimulate gastric secretion. Two normal rabbits received the same amount of toxin. The starved rabbits died before the controls. Starving the rabbits lowered their resistance to the toxin, or absorption of the toxin was more rapid in the empty stomachs. No experiments were made to determine which factor predominates. If the latter explanation is the

28. Forsman: Beiträge zur Kenntnis der Bakteriologie des Botulismus, Lundi Universitets Arsskrift, 1900; Abstr. Centralbl. f. Bakteriol. **29**:541, 1901.

true one then the amount of nontoxic food eaten by those at meals causing outbreaks of botulism may account for some of the variation in time of the appearance of the symptoms in the patients. The gastric juice apparently has no effect on the toxin. The results obtained (Table 7) suggest that in some outbreaks of botulism the amount of nontoxic food eaten may account for some of the variation in the time of the appearance of the symptoms in the victims and the degree of illness.

TABLE 7.—Results of Starving and Subsequent Empty Stomach on Rate of Absorption of Toxin in Rabbit

Rabbit	Amount Toxin	Condition of Stomach	Results
1	4 c.c.	Full stomach	Dead in 144 hours
2	4 c.c.	Full stomach	Dead in 48 hours
3	4 c.c.	Starved 48 hours	Dead in 35 hours
4	4 c.c.	Starved 48 hours	Dead in 18 hours

Experiments were made to determine the effect of different human foods on the toxin of *C. botulinum*. It was thought that some foods might be more effective than others in slowing down the rate of absorption of the toxin. These experiments were designed to determine if the various foods afforded protection against the action of the toxin, if this protection was as great in the stomach as in subcutaneous injections and whether the protection was due to a neutralization of the toxin or to a slowing down of the rate of absorption.

FATS AND OILS

Kempner and Schepilewsky [29] state that butter and emulsified oil neutralize about twice the lethal dose of toxin for guinea-pigs when the fat and toxin are mixed and injected subcutaneously. McCaskey urges the use of "castor oil or some other laxative fat, for the double purpose of clearing out the ingested toxin, which is largely formed under saprophytic conditions, and of lowering or destroying the virulence by combination of fats." In consideration of these statements it seemed advisable to determine the extent of the protection afforded by the use of fats, the nature of this protection and if the protection afforded by different fats varied. Typical animal, vegetable and mineral fats and oils were used. The experiments described here are rather limited but the results obtained furnish the basis for certain conclusions which will be given under each experiment.

OLIVE OIL

Experiment to Determine Whether Olive Oil Protects Against the Action of the Toxin of C. Botulinum.—Different amounts of olive oil

29. Kempner and Schepilewsky: Ueber antitoxische Substanzen gegenüber dem Botulismusgift, Ztschr. f. Hyg. **27**:213, 1898.

and a Type A toxin filtrate were used. The oil and toxin were placed in test tubes, emulsified by vigorous shaking and incubated one hour. The tubes were shaken several times during the incubation period. Injections were made subcutaneously into guinea-pigs. The results obtained (Table 8) show that guinea-pigs are protected from the action of the toxin of *C. botulinum* when the toxin and oil are emulsified in a test tube, incubated one hour and injected subcutaneously. Three c.c. of the oil protected against the action of 3 M. L. D. of the toxin but not against 4 M. L. D.

TABLE 8.—Effect of Olive Oil Against Action of Toxin of C. Botulinum When the Two Are Emulsified, Incubated and Injected Subcutaneously?

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Olive Oil	Results
1	275	3 M. L. D.	.....	Dead, 20 hours
2	315	3 M. L. D.	3 c.c.	Lived
3	310	3 M. L. D.	6 c.c.	Lived
4	300	4 M. L. D.	3 c.c.	Dead, 70 hours
5	300	5 M. L .D.	5 c.c.	Dead, 96 hours

Experiments were made to determine whether the protection afforded by the olive oil was due to a neutralization of the toxin or to a slowing down of the rate of absorption. We assumed that if the protection afforded by the olive oil is due to a purely physical slowing down of the rate of absorption the following statements would prove to be true.

1. If the mixture, after incubation, is centrifuged the toxin in the water should not show any appreciable reduction in strength.

2. Emulsifying the toxin oil mixture several seconds should be just as effective as incubating several hours.

3. In intraperitoneal injections the protection afforded by the oil would be much less than that in subcutaneous injections and not such as could be accounted for by the difference in the M.L.D. for the two types of injections, and those receiving the oil-toxin mixture should die almost as soon as the controls. In intraperitoneal injections the rate of absorption is much greater.

Experiment to determine whether the strength of the toxin of C. botulinum is reduced after exposure to olive oil.—The same toxin and olive oil were used as in the preceding experiment. The toxin and olive oil were emulsified, incubated two hours and then centrifuged until the oil was free of water. The water was injected subcutaneously in guinea-pigs. The results obtained (Table 9) indicate that the strength of the toxin is affected slightly if at all by exposure to olive oil.

The experiment was repeated, with the exception that the injections were made intraperitoneally. The results obtained agree with those in the preceding experiment. The toxin control pig was dead in fifteen hours; the exposed toxin pig was dead in twenty-four hours and the mixture control pigs were dead in eighty-eight hours.

TABLE 9.—Effect of Olive Oil on the Strength of the Toxin of C. Botulinum

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Remarks	Result
1	365	3 M. L. D.	.....	Toxin control.....	Dead, 20 hours
2	300	3 M. L. D.	6 c.c.	Mixture control.....	Lived
3	315	3 M. L. D.	3 c.c.	Mixture control.....	Lived
4	325	3 M. L. D.	0 c.c.	Exposed toxin.....	Dead, 40 hours

Experiment to determine whether emulsifying the toxin and olive oil and injecting immediately is just as effective in protecting against the action of the toxin as incubating two hours before injecting.—The same toxin and olive oil was used as in the preceding experiment. The toxin and olive oil were placed in a test tube, shaken vigorously for 30 seconds and then injected subcutaneously into guinea-pigs. The control mixture was incubated two hours. The results obtained (Table 10) indicate that the incubation does not increase the protection afforded by the olive oil.

TABLE 10.—Results of Experiment to Determine Whether Emulsifying Toxin and Olive Oil and Injecting Immediately Is Just as Effective in Protecting Against Action of Toxin as Incubating Two Hours Before Injecting

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Remarks	Result
1	365	5 M. L. D.	.....	Toxin control.....	Dead, 20 hours
2	275	5 M. L. D.	6 c.c.	Mixture incubated.....	Dead, 46 hours
3	295	5 M. L. D.	6 c.c.	Mixture not incubated.....	Dead, 50 hours
4	330	5 M. L. D.	6 c.c.	Mixture not incubated.....	Dead, 56 hours

The results of the above experiment with the olive oil convinced us that olive oil does not neutralize the toxin of *C. botulinum* and the experiments were discontinued. The protection afforded by the olive oil is probably due to a slowing down of the rate of absorption. It takes some time for the water containing the toxin to separate from the oil. This slowing down of the rate of absorption is sufficient to protect the guinea-pig from small amounts of toxin.

Experiment to determine whether olive oil protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.—Each rabbit was force fed 2.5 c.c. of a toxic filtrate, Type B. Ten c.c. of olive oil was force fed immediately after the toxin and at repeated intervals. The results obtained (Table 11) indicate that under the conditions of

this experiment olive oil affords a slight protection against the action of the toxin in the stomach of the rabbit. This protection is probably due to a slowing down of the rate of absorption of the toxin. The 2.5 c.c. of toxic filtrate used contained from 2 to 3 M. L. D. of toxin. It is possible that if 1 M. L. D. of toxin were used the protection afforded by the olive oil would be sufficient to save the life of the animal. Since the protection afforded by the olive oil is so slight and is of a physical nature, it is doubtful if it would have had any effect on the course of the disease if the treatment had been begun several hours after the toxin was administered.

TABLE 11.—Effect of Olive Oil on the Action of Toxin of C. Botulinum in Stomach of Rabbit When Force Fed Immediately After Toxin and at Repeated Intervals

Rabbit	Weight, Gm.	Amount Toxin	Amount Oil	Hours Feeding Oil After Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,260	2.5 c.c.	10 c.c.	0, 2, 18, 25	Dead, 39 hours
4	1,860	2.5 c.c.	10 c.c.	0, 2, 18, 25	Dead, 50 hours

LIQUID PETROLATUM

The experiments made with olive oil were repeated with liquid petrolatum as the neutralizing agent. The results obtained are similar to those obtained with olive oil. In experiments made by us the liquid petrolatum seemed to give less protection than the olive oil against the action of the toxin in subcutaneous injections and more protection than the olive oil in the stomach of the rabbit. It is assumed that the protection afforded by the liquid petrolatum is of the same nature as the protection afforded by the olive oil.

Experiment to determine whether liquid petrolatum protects against the action of the toxin of C. botulinum when the two are emulsified, incubated and injected subcutaneously into guinea-pigs.—The liquid petrolatum and a Type A toxic filtrate were mixed in a test tube, emulsified by vigorous shaking and incubated two hours. The mixture was shaken several times during the incubation period. The injections were made subcutaneously into guinea-pigs. The results obtained (Table 12) show that liquid petrolatum protects to a limited extent against the action of the toxin of *C. botulinum*. The guinea-pigs receiving the toxin-liquid petrolatum mixture lived several days longer than the toxin control.

Experiment to determine whether liquid petrolatum protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.—

This experiment was conducted in the same manner as the similar test with olive oil and the results obtained were approximately the same as with the olive oil. The animal receiving the liquid petrolatum lived eleven hours longer than the animal receiving the olive oil, a slight difference which we believe has no significance. The details of this experiment have no particular significance and are omitted for the sake of brevity. We hoped that a mineral oil which is unaffected by the action of the gastric juice would be more effective against the action of the toxin than a vegetable oil but such did not prove to be the case.

TABLE 12.—Effect of Liquid Petrolatum Against Action of Toxin of C. Botulinum When the Two Are Emulsified, Incubated and Injected Subcutaneously

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Oil	Results
1	600	3 M. L. D.	.....	Dead, 29 hours
2	550	3 M. L. D.	3 c.c.	Dead, 170 hours
3	575	3 M. L. D.	6 c.c.	Dead, 166 hours

BUTTER

Our experiments with butter indicate that it affords less protection against the action of the toxin of *C. botulinum* than olive oil or liquid petrolatum. This is probably due to some physical difference between the butter and the oils. The water containing the toxin seemed to separate from the butter more rapidly than from the oils. If the protection against the toxin afforded by fats depends upon a slowing down of the rate of absorption then the amount of protection afforded by any fat depends on the rate of separation of the water from the fat.

TABLE 13.—Effect of Butter Against Action of Toxin of C. Botulinum When the Two Are Emulsified, Incubated and Injected Subcutaneously Into Guinea-Pigs

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Butter	Results
1	450	3 M. L. D.	.....	Dead, 21 hours
2	250	3 M. L. D.	3 c.c.	Dead, 35 hours
3	450	3 M. L. D.	6 c.c.	Dead, 50 hours

Experiment to determine whether butter protects against the action of the toxin of C. botulinum when the two are emulsified, incubated and injected subcutaneously into guinea-pigs.—The butter was melted, emulsified with a type B filtrate and incubated two hours. The emulsion was shaken several times during the incubation period. Injections were made subcutaneously into guinea-pigs. The results obtained (Table 13) indicate that butter has a slight retarding action on the toxin of *C. botulinum*. We believe this action is due to a slowing down

of the rate of absorption and that butter does not protect against the toxin as well as olive oil because the emulsion breaks down more rapidly.

MILK, EGG WHITE, EGG YOLK, SUGAR, BRAIN, GELATIN

Kempner and Schepilewsky [30] state that the brain tissue of a guinea-pig will neutralize from 3 to 4 M. L. D. of toxin if the brain tissue and toxin are mixed in a test tube and that some protection is afforded by the brain tissue if injected separately from the toxin. Our experiments indicate that the brain tissue of the sheep has no special affinity for the toxin of *C. botulinum* and in "in vitro" injections affords little or no protection.

Experiment to determine whether milk, egg white, egg yolk, sugar, brain tissue and gelatin afford as great protection against the action of the toxin of C. botulinum as olive oil.—The brain tissue was ground up and squeezed through cheese cloth. A type B toxin filtrate was used. All mixtures were shaken thoroughly, incubated 1 hour and injected subcutaneously into guinea-pigs. The results obtained (Table 14) indicate that in subcutaneous injections the protection afforded by these food substances is not equal to that of olive oil.

TABLE 14.—RESULT OF AN EXPERIMENT TO DETERMINE WHETHER MILK, EGG WHITE, EGG YOLK, SUGAR, BRAIN TISSUE AND GELATIN AFFORD AS GREAT PROTECTION AS OLIVE OIL AGAINST ACTION OF TOXIN OF C. BOTULINUM

Guinea-Pig	Amount Toxin	Amount Neutralizing Agent	Results
1	3 M. L. D.	.....	Dead in 20 hours
2	3 M. L. D.	3 c.c. olive oil.....	Lived
3	4 M. L. D.	3 c.c. olive oil.....	Dead in 70 hours
4	2 M. L. D.	4 c.c. milk.....	Dead in 20 hours
5	2 M. L. D.	1 c.c. 25% solution glucose.....	Dead in 42 hours
6	2 M. L. D.	3 c.c. egg white.....	Dead in 40 hours
7	2 M. L. D.	3 c.c. egg yolk.....	Dead in 40 hours
8	2 M. L. D.	3 gm. sheep brain.....	Dead in 36 hours
9	3 M. L. D.	3 c.c. 20% gelatin in water.....	Dead in 35 hours

VINEGAR

A number of outbreaks of botulism have followed the eating of salads containing the poisonous food. We considered it advisable to determine whether any of the ingredients of ordinary salad dressing would affect the action of the toxin. The three common ingredients of salad dressings are olive oil, egg and vinegar. We have already shown that olive oil affords some protection against the action of the toxin of *C. botulinum* and that egg affords little or no protection. We record here our experiments with vinegar.

Experiment to determine whether vinegar affords protection against the action of the toxin of C. botulinum when the two are mixed in a test tube, incubated two hours and injected subcutaneously into guinea-

30. Kempner and Schepilewsky: Ueber antitoxische Substanzen gegenüber dem Botulismusgift, Ztschr. f. Hyg. **27**:213, 1898.

pigs.—A Type B toxin filtrate and apple vinegar were used. The toxin and vinegar were mixed in a test tube and incubated two hours and injected subcutaneously in guinea-pigs. The results obtained (Table 15) show that 3 c.c. of the apple vinegar used protected against the action of a 4 M. L. D. of toxin.

It was found that the vinegar caused considerable necrosis, and the possibility of this accounting for the protection against the toxin was considered. It was thought that the necrosis might slow down the rate of absorption and the necrotic cells absorb some of the toxin.

TABLE 15.—Effect of Vinegar Against Action of Toxin of C. Botulinum When the Two Are Mixed, Incubated Two Hours and Injected Subcutaneously

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Vinegar	Result
1	415	4 M. L. D.	.....	Dead in 15 hours
2	400	.....	3 c.c.	Lived
3	405	4 M. L. D.	3 c.c.	Dead in 84 hours
4	400	4 M. L. D.	3 c.c.	Lived

TABLE 16.—Results of an Experiment to Determine Whether the Protection Afforded by Vinegar Against Action of Toxin of C. Botulinum Is Due to Necrosis of Tissues or to Acetic Acid Present in Vinegar

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Vinegar	Remarks	Results
1	415	4 M. L. D.	.....	.....	Dead, 15 hours
2	430	4 M. L. D.	3 c.c.	Neutralized with sodium hydroxid just before injecting.....	Lived
3	415	4 M. L. D.	3 c.c.	Neutralized before adding to toxin	Lived
4	275	8 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 27 hours
5	280	20 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 15 hours
6	275	200 M. L. D.	1 c.c.	Neutralized before adding to toxin	Dead, 15 hours

Experiment to determine whether the protection afforded by vinegar against the action of the toxin of C. botulinum is due to a neutralization of the toxin or to a necrosis of the tissues or to the acetic acid present in the vinegar.—Vinegar neutralized with sodium hydroxid causes little or no necrosis. The toxin filtrate and vinegar were mixed, incubated two hours, neutralized with normal sodium hydroxid and injected subcutaneously into guinea-pigs. To determine whether neutralized vinegar protects against the action of the toxin, vinegar was neutralized with normal sodium hydroxid, mixed with the toxin, incubated and injected subcutaneously into guinea-pigs. The results obtained (Table 16) indicate that the protection afforded by the vinegar is not due to the necrosis of the tissues. They also indicate that the action on the toxin is not due to the acid in the vinegar since the neutralized vinegar also protects against the action of the toxin.

Experiment to determine whether acetic acid, sodium acetate and sodium hydroxid will protect against the action of the toxin of C.

botulinum when mixed with the toxin incubated and injected subcutaneously into guinea-pigs.—A Type B toxin filtrate was used. The amount of normal sodium hydroxid used was the same as that used to neutralize the 3 c.c. of vinegar. The amount of acetic acid used was the amount required to neutralize the sodium hydroxid. Controls with acetic acid and normal sodium hydroxid were not made. The mixtures were incubated two hours before being injected subcutaneously into guinea-pigs. The results obtained (Table 17) show that acetic acid and sodium acetate do not neutralize the toxin of *C. botulinum*. The guinea-pig receiving the sodium hydroxid-toxin mixture neutralized just before injecting lived nine days. The animal receiving sodium hydroxid toxin mixture unneutralized died in fourteen days. The death of this animal may have been due to the alkali rather than to the toxin, as the whole lower part of the body was greatly swollen. The animal receiving the sodium hydroxid neutralized with acetic acid before the toxin was added died. The protection afforded by the sodium hydroxid apparently is not due to a slowing down of the rate of absorption of the toxin as there was no evidence of necrosis in the animal living nine days. The results obtained with the sodium hydroxid suggest that it neutralizes the action of the toxin to some extent.

TABLE 17.—Effect of Acetic Acid, Sodium Acetate and Sodium Hydroxid Against Action of Toxin of C. Botulinum When Mixed with Toxin, Incubated and Injected Subcutaneously

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Neutral Agent and Remarks	Results
1	275	4 M. L. D.	.....	Dead, 15 hours
2	275	4 M. L. D.	1 c.c. salt solution.....	Dead, 15 hours
3	285	4 M. L. D.	2.4 c.c. normal acetic acid. Neutralized with normal sodium hydroxid just before injecting.....	Dead, 36 hours
4	290	4 M. L. D.	2.4 c.c. normal acetic acid. Neutralized with normal sodium hydroxid before adding to toxin.....	Dead, 36 hours
5	300	4 M. L. D.	2.4 c.c. normal sodium hydroxid.....	Dead, 14 days
6	400	4 M. L. D.	2.4 c.c. normal sodium hydroxid neutralized with normal acetic acid just before injecing	Dead, 9 days
7	310	4 M. L. D.	0.04 gm. sodium acetate.....	Dead, 36 hours
8	325		0.04 gm. sodium acetate.....	Lived

These experiments have not determined the active agent in the protection afforded by vinegar or vinegar neutralized with normal sodium hydroxid. We apparently have eliminated acetic acid as a factor in the first case and sodium acetate as a factor in the second case. Since sodium hydroxid reduces the virulence of the toxin, we have not eliminated the possibilty of the protection afforded by the vinegar being due to necrosis of the tissues and the protection afforded by the neutralized vinegar being due to some action of the sodium hydroxid. As we have shown that sodium hydroxid neutralized with acetic acid does not reduce the virulence of the toxin we believe that the protection afforded by the vinegar is not due entirely to necrosis but to some factor

not determined by us. A qualitative test for alcohol was positive. Our experiments were discontinued at this point. Armstrong, Story and Scott state that alcohol neutralizes the toxin of *C. botulinum*. The small amount of alcohol in the vinegar may account for its neutralizing action on the toxin. Further experiments with vinegar should be made. In this connection it is interesting to note that Dickson,[8] quoting Schreiber and Hirschfeldt, reports two outbreaks of food poisoning following the eating of herring preserved in vinegar. Also, some of the outbreaks of botulism in this country followed the eating of salads containing vinegar and olive oil.

TABLE 18.—EFFECT OF VINEGAR AGAINST ACTION OF TOXIN OF C. BOTULINUM IN STOMACH OF RABBIT WHEN FORCE FED IMMEDIATELY AFTER TOXIN AND AT REPEATED INTERVALS

Rabbit	Weight, Gm.	Amount Toxin	Amount Vinegar	Hours After Feeding Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,260	2.5 c.c.	10 c.c. water	0, 2, 18, 25	Dead, 39 hours
4	1,465	2.5 c.c.	5 c.c. vinegar	0, 2, 18	Lived

Experiment to determine whether vinegar protects against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.—A Type B toxin filtrate was used. The amount given was approximately 2 M. L. D. The rabbits were fed 5 c.c. vinegar at each treatment, receiving a total amount of 15 c.c. The results obtained (Table 18) indicate that vinegar affords some protection against the action of the toxin in the stomach of the rabbit.

GRAM'S IODIN SOLUTION

Experiment to determine whether Gram's solution protects against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.—A Type B toxin filtrate was used. The Gram solution was mixed with the toxin, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 19) indicate that this solution protects against the action of the toxin of *C. botulinum*. A guinea-pig was saved from the effects of 8 M. L. D. of toxin by 0.1 c.c. of Gram's solution.

Experiment to determine whether Gram's solution will protect against the action of the toxin of C. botulinum when injected separately from the toxin.—A Type B toxin was used. Repeated injections of Gram's solution were made on the opposite side of the body of the guinea-pigs from the toxin. The injections were begun before or at the same time the toxin was injected. To prevent the iodin causing

necrosis of the tissues, 70 mg. of corn starch were added to each cubic centimeter of the Gram solution. The iodin injections were repeated at three hour intervals. The results obtained (Table 20) indicate that Gram's solution when injected separately from the toxin offers no protection.

TABLE 19.—EFFECT OF GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF C. BOTULINUM WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY INTO GUINEA-PIGS

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Gram's Solution	Results
1	420	4 M. L. D.	.....	Dead, 28 hours
2	345	8 M. L. D.	.....	Dead, 15 hours
3	275	4 M. L. D.	.....	Dead, 15 hours
4	450	4 M. L. D.	1.5 c.c.	Lived
5	260	4 M. L. D.	0.8 c.c.	Lived
6	275	4 M. L. D.	0.6 c.c.	Lived
7	270	4 M. L. D.	0.4 c.c.	Lived
8	260	4 M. L. D.	0.1 c.c.	Lived
9	345	8 M. L. D.	0.1 c.c.	Lived
10	335	20 M. L. D.	0.1 c.c.	Dead in 40 hours
11	320	200 M. L. D.	0.1 c.c.	Dead in 15 hours

TABLE 20.—EFFECT OF GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF C. BOTULINUM WHEN INJECTED SEPARATELY FROM THE TOXIN

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Gram's Solution	Hours Injected After Toxin	Results
1	315	2 M. L. D.	.....	.....	Dead, 35 hours
2	315	2 M. L. D.	4 c.c.	0, 3, 5, 9	Dead, 29 hours
3	280	2 M. L. D.	4 c.c.	3, 0, 3, 5, 9	Dead, 31 hours

TABLE 21.—RESULT OF EXPERIMENT TO DETERMINE WHETHER THE PROTECTION AFFORDED BY GRAM'S SOLUTION AGAINST ACTION OF TOXIN OF C. BOTULINUM IS DUE TO THE NECROSIS OF THE TISSUE, TO THE POTASSIUM IODID OR TO THE IODIN

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Neutralizing Agent and Remarks	Results
1	335	4 M. L. D.	.....	Dead, 15 hours
2	450	4 M. L. D.	1.5 c.c. Gram's solution.....	Lived
3	465	4 M. L. D.	1.5 c.c. Gram's solution, starch added just before injecting.....	Lived
4	460	4 M. L. D.	1.5 c.c. Gram's solution, starch added before the toxin.....	Lived
5	450	4 M. L. D.	3 c.c. saturated solution of iodin.....	Lived
6	430	4 M. L. D.	1.5 c.c. 2% potassium iodid.....	Dead, 40 hours
8	435	4 M. L. D.	105 mg. corn starch in salt solution.....	Dead, 28 hours
7	210	4 M. L. D.	4.5 c.c. 2% potassium iodid.....	Dead, 27 hours

Experiment to determine whether the protection afforded by Gram's solution against the action of the toxin of C. botulinum is due to the necrosis of the tissues, to the potassium iodid or to theiodin.—A Type B toxin filtrate, a 2 per cent. solution of potassium iodid and a saturated aqueous solution of iodin were used. Seventy mg. of corn starch were added to each cubic centimeter of the iodin solution to prevent necrosis of the tissues. The toxin and solutions were mixed, incubated two hours

and injected subcutaneously into guinea-pigs. The animals receiving the Gram solution, the Gram iodin starch mixture and the saturated solution of iodin lived. The animal receiving the potassium iodid died about the same time as the controls. The results obtained (Table 21) show that the protection afforded by Gram's solution is not due entirely to necrosis of the tissues or to the potassium iodid present, but to the iodin.

Experiment to determine whether Gram's solution neutralized with corn starch is just as effective as unneutralized Gram's solution in protecting against the action of the toxin of C. botulinum.—A Type B toxin filtrate was used. To neutralize the action of the Gram's solution on the tissues, 70 mg. of corn starch was added to each cubic centimeter. The toxin was mixed with the solutions, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 22) indicate that the addition of starch to the Gram solution slightly reduces its protective action against the toxin. The increased protection afforded by the unneutralized Gram's solution may be due to its action on the tissues.

TABLE 22.—Results of Experiment to Determine Whether Gram's Solution Neutralized with Corn Starch Is Just as Effective as Unneutralized Gram's Solution in Protecting Against Action of Toxin of C. Botulinum

Guinea-Pig	Weight	Amount Toxin	Amount Neutralizing Agent	Result
1	420	4 M. L. D.	.....	Dead, 28 hours
2	275	4 M. L. D.	.....	Dead, 15 hours
3	260	4 M. L. D.	0.1 c.c. Gram's solution.....	Lived
4	345	8 M. L. D.	0.1 c.c. Gram's solution.....	Lived
5	235	20 M. L. D.	0.1 c.c. Gram's solution.....	Dead, 40 hours
6	320	200 M. L. D.	0.1 c.c. Gram's solution.....	Dead, 15 hours
7	405	4 M. L. D.	0.4 c.c. neutralizing Gram's solution	Lived
8	380	8 M. L. D.	0.4 c.c. neutralizing Gram's solution	Dead, 110 hours
9	360	20 M. L. D	0.4 c.c. neutralizing Gram's solution	Dead, 18 hours
10	285	200 M. L. D.	0.4 c.c. neutralizing Gram's solution	Dead, 15 hours

TABLE 23.—Effect of Gram's Solution Against Action of Toxin of C. Botulinum in Stomach of Rabbit When Force Fed Immediately After Toxic Culture and at Repeated Intervals

Rabbit	Amount Toxic Culture	Amount Gram's Solution	Hours After Toxin	Results
1	6 c.c.	.....	.....	Dead, 17 hours
2	6 c.c.	.....	.....	Dead, 30 hours
3	6 c.c.	4 c.c.	0	Dead, 3 hours
4	6 c.c.	4 c.c.	0, 2, 4	Lived

Experiment to determine whether Gram's solution will protect against the action of the toxin of C. botulinum in the stomach of the rabbit when force fed immediately after a toxic culture and at repeated intervals.—Each rabbit received 6 c.c. of a toxic meat culture of *C. botulinum* Type B. Four c.c. of Gram's solution was used at each

treatment. This is an extreme dose and will kill some of the rabbits before the toxin has time to act. We did not test the effect of a Gram iodin-starch solution. The Gram solution is a strong disinfectant and should destroy the organisms reached as well as the toxin. In our short series of experiments one of the rabbits receiving the Gram solution after the toxin lived, indicating that the iodin has some neutralizing action on the toxin in the stomach of a rabbit (Table 23).

LIQUID SOAP

We have already shown that sodium hydroxid has a neutralizing action on the toxin of *C. botulinum*. Since soap contains an alkali and may be used in the preparation of enemas, we undertook to determine whether liquid soap would protect against the action of the toxin of *C. botulinum*. The soap used did not change the color of either litmus paper or phenolphthalein paper.

TABLE 24.—EFFECT OF LIQUID SOAP AGAINST ACTION OF TOXIN OF C. BOTULINUM WHEN THE TWO ARE MIXED, INCUBATED AND INJECTED SUBCUTANEOUSLY

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Soap	Remarks	Results
1	275	4 M. L. D.	.....	.....	Dead, 15 hours
2	305	4 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
3	315	8 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
4	330	20 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived
5	325	200 M. L. D.	1 c.c.	3 c.c. salt solution added just before injecting...	Lived

Experiment to determine whether liquid soap will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.—A Type B. toxin filtrate was used. Subcutaneous injection of the soap caused considerable necrosis and occasionally death. The addition of salt solution was found to prevent this, and in these experiments 3 c.c. of physiologic sodium chlorid solution were added to each cubic centimeter of soap used. The salt solution was added to the toxin-soap mixture after the incubation period. The toxin-soap mixtures were incubated two hours, the salt solution added, and then injected subcutaneously into guinea-pigs. The results obtained (Table 24) show that 1 c.c. of the liquid soap used protected a guinea-pig from at least 20 M. L. D. of toxin. No attempt was made to determine the active agent in the neutralization of the toxin, but we believe that the alkali in the soap neutralized the toxin. We found that glycerin has no effect on the toxin.

Experiments to determine the action of soap on the toxin in the stomach of rabbits was begun but were not carried far enough to war-

rant description. In our preliminary experiments in force feeding soap, the animals died in a few hours from the effects of the soap. Experiments should be made to determine whether the soap can be diluted sufficiently not to injure the rabbit fatally and retain its action on the toxin. The action of the soap on the toxin in the intestines should also be demonstrated. Experiments with soap might lead to some treatment of value.

MISCELLANEOUS FEEDING EXPERIMENTS

Drawing any conclusions from the results of a short series of feeding experiments is very unsatisfactory. This is particularly true when feeding small amounts of toxin and basing the conclusions on the time of appearance of the symptoms or the time of death. However, these are conditions that are difficult to avoid. We are dealing with a powerful toxin and we cannot hope for more than a slight protection from any nonspecific treatment. In subcutaneous injections the lethal dose can be accurately determined and remains fairly constant for animals of the same weight. This is not true in feeding experiments. As a result of our experiment to determine the effect of a full rabbit stomach on the action of the toxin, we believe that the amount of food in the rabbit stomach at the time the animal is fed will affect the time of death. Also, if the feeding tube penetrates the mass of food in the stomach and the toxin is deposited in the center of the food mass, absorption will be delayed. Some rabbits readily take food after the toxin is fed, others eat sparingly or not at all. In order to discount these factors, we used two toxin controls and sufficient toxin to insure death in less than forty-eight hours. Presumably any animal living longer than forty-eight hours was protected to some extent by the substance being tested. The amount of toxin used was such that in most cases the toxin controls were dead in fifteen hours. While the animals living longer than forty-eight hours apparently were protected to some extent, it is possible that some of the animals dying between twenty-four and forty-eight hours were also slightly protected.

We believe that with most of the substances used by us the main factor in the protection afforded is a slowing down of the rate of absorption. We have shown in subcutaneous injection that by mixing the toxin with olive oil, the rate of absorption is slowed down to such an extent that guinea-pigs will resist three lethal doses. The rate of absorption of the toxin from the stomach affects the time of the appearance of symptoms and of death. And, in case a small amount of toxin is ingested, any slowing down of the rate of absorption may prevent death.

When it became evident that our investigations must be terminated, we carried out a number of feeding experiments. We had already shown that some of the substances used had no effect on the toxin when mixed with it and injected subcutaneously. It was thought, however, that they might delay the appearance of the symptoms when force fed into the stomach immediately after the toxin. The results obtained would, at least, have some bearing on our belief that the amount and kind of food taken with the toxin materially affects the time of appearance and severity of the symptoms. Also, these non-neutralizing substances might have more effect on the toxin after coming in contact with and being altered by the gastric juice. Other of these substances had been shown to protect against the action of the toxin in subcutaneous injections. It was thought that these might not have any effect on the toxin in the stomach as a result of being altered by contact with the gastric juice before coming in contact with the toxin.

Experiment to determine the effect of milk, turpentine, alcohol, a proprietary nerve tonic and water on the toxin in the stomach of the rabbit when force fed immediately after the toxin and at repeated intervals.—About 2 M. L. D. of Type B toxin was used; this required 2.5 c.c. of the filtrate. We have shown that milk does not neutralize or protect against the action of the toxin in subcutaneous injections. Armstrong, Story and Scott have shown that alcohol will protect against the action of the toxin when the two are mixed and injected subcutaneously. We used a 30 per cent. solution of alcohol. While testing the protective properties of miscellaneous substances it was suggested that the effects of a proprietary nerve tonic be determined. According to the label this tonic contained 14 per cent. alcohol, and each fluid ounce contained 8 grains sodium glycerophosphate, 4 grains calcium glycerophosphate, 4 grains potassium glycerophosphate, $\frac{1}{60}$ grain strychnin glycerophosphate, $\frac{1}{16}$ grain lecithin and $\frac{1}{30}$ grain avenin. The tonic was used without diluting. These substances were force fed immediately after the toxin and at repeated intervals. The results obtained (Table 25) indicate that either numerous substances have a slight effect on the action of the toxin in the stomach of the rabbit, or that none of the substances used had any effect, and the results obtained simply represent individual variation in resistance to the toxin. Rabbits do show considerable variation in resistance to force fed toxin. We believe, however, that our results indicate something more than individual variation or error in technic. In experiments of this kind in which we are endeavoring to determine or measure slight effects and in which all the factors cannot be controlled, long series of experiments should be made. We have not had an opportunity to do this.

TABLE 25.—Results of Experiments to Determine Effect of Milk, Turpentine, Alcohol, a Proprietary Nerve Tonic and Water on the Toxin of C. Botulinum in the Stomach of Rabbit When Force Fed Immediately After Toxin and at Repeated Intervals

Rabbit	Weight, Gm.	Amount Toxin	Amount Neutralizing Agent	Injections Hours After Toxin	Results
1	2,300	2.5 c.c.	.....	.....	Dead, 15 hours
2	1,725	2.5 c.c.	.....	.....	Dead, 15 hours
3	1,675	2.5 c.c.	10 c.c. milk.....	0, 2, 18, 25	Dead, 87 hours
4	1,575	2.5 c.c.	5 c.c. tonic.....	0, 2, 18, 25	Lived
5	1,800	2.5 c.c.	4 c.c. turpentine..	0, 5	Dead, 80 hours
6	2,000	2.5 c.c.	4 c.c. 30% alcohol	0, 5	Dead, 73 hours
7	1,360	2.5 c.c.	15 c.c. water.....	0, 2, 18, 25	Dead, 39 hours

EPINEPHRIN

Marie [33] states that epinephrin neutralizes the soluble toxins of tetanus and diphtheria. He shows that epinephrin will protect against lethal doses of the toxins both in "in vitro" and in "in vivo" experiments. Our experiments indicate that epinephrin chlorid affords some protection against lethal doses of the toxin of *C. botulinum* when the two are mixed and injected subcutaneously.

Experiment to determine whether epinephrin chlorid will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously into guinea-pigs.—A Type B toxin filtrate and the ordinary commercial epinephrin chlorid solution, 1:1,000, were used. The toxin and epinephrin solution were mixed, incubated two hours and injected subcutaneously in guinea-pigs. The results obtained (Table 26) indicate that epinephrin chlorid solution has some neutralizing action on the toxin of *C. botulinum*. Experiments should be made to determine whether the action of epinephrin on the body influences the course of the disease.

TABLE 26.—Effect of Epinephrin Chlorid Against Action of Toxin of C. Botulinum When the Two Are Mixed, Incubated and Injected Subcutaneously

Guinea-Pig	Weight, Gm.	Amount Toxin	Amount Epinephrin	Results
1	175	3 M. L. D.	.....	Dead, 18 hours
2	200	.....	0.1 c.c.	Lived
3	200	3 M. L. D.	0.1 c.c.	Dead, 42 hours
4	210	3 M. L. D.	0.2 c.c.	Dead, 60 hours

POTASSIUM PERMANGANATE

Experiment to determine whether potassium permanganate will protect against the action of the toxin of C. botulinum when the two are mixed, incubated and injected subcutaneously in guinea-pigs.—A

33. Marie: Du mode d'action de l'adrenaline vis a vis des toxines solubles, Compt. rend. Soc. de biol. **82**: 1919; Du mode d'action de l'adrenaline sur les toxines bacteriennes, Ann. de l'Inst. Pasteur **33**:645, 1919.

Type A toxin filtrate and a 1 per cent. water solution of potassium permanganate were used. The toxin and potassium permanganate solution were mixed, incubated two hours and injected subcutaneously into guinea-pigs. The results obtained (Table 27) indicate that 1 c.c. of a 1 per cent. solution of potassium permanganate will protect a guinea-pig from at least 6 M. L. D. of toxin. The potassium permanganate causes considerable necrosis of the tissues. No attempt was made to determine if the necrosis is a factor in the protection afforded by the potassium permanganate.

TABLE 27.—Effect of Potassium Permanganate Against Action of Toxin of C. Botulinum When the Two Are Mixed, Incubated and Injected Subcutaneously

Guinea-Pig	Amount Toxin	Amount Potassium Permanganate	Result
1	2 M. L. D.	.....	Dead, 36 hours
2	2 M. L. D.	1 c.c.	Dead, 15 days
3	3 M. L. D.	1 c.c.	Lived
4	4 M. L. D.	1 c.c.	Lived
5	6 M. L. D.	1 c.c.	Lived

CONCLUSIONS

1. Spoiled foods containing gas may appear to be boiling for several minutes before the true boiling point is reached. We recommend that all suspected food be subjected to vigorous boiling for at least thirty minutes before being tasted.

2. Spoiled canned foods giving the appearance of boiling for seven minutes and subjected to actual boiling for four minutes are not safe to eat. Spoiled canned foods exposed to a temperature of 80 C. for one hour may appear to be boiling part of the time and not be safe to eat.

3. We may expect to have outbreaks of botulism following the eating of insufficiently cooked spoiled foods.

4. The heat resistance of the disease producing power of different kinds of spoiled canned foods containing *C. botulinum* and its toxin has not been determined and probably will be found to vary.

5. There have been no recorded outbreaks of botulism in this country without a history of preserved foods having been eaten.

6. There is no evidence that infection in man ever follows the ingestion of toxin free organisms of *C. botulinum*.

7. There is no evidence that infection in man ever follows the ingestion of the toxin and organisms of *C. botulinum*.

8. Botulism does not result from the ingestion of small numbers of toxin free spores.

9. The disease producing power of an old can of spoiled beans containing *C. botulinum* and its toxin can be destroyed by an exposure to temperatures that rarely if ever destroy the spores of *C. botulinum*.

10. Rabbits can be saved from the effects of feeding 2 M. L. D. of a toxic culture of *C. botulinum* by the intravenous injection of the homologous antitoxin as soon as the symptoms appear. Such rabbits cannot be saved if the antitoxin treatment is delayed until the symptoms are well advanced.

11. In outbreaks of botulism, as soon as the first case develops, a polyvalent immune serum should be injected intravenously in all those who have partaken of the suspected meal. This treatment should materially decrease the death rate.

12. The contents of a full normal rabbit stomach does not neutralize the toxin of *C. botulinum* but it apparently reduces the action of the toxin to some extent by slowing down or preventing its absorption.

13. Fats and oils do not neutralize the toxin of *C. botulinum*.

14. Fats and oils will protect against the action of the toxin of *C. botulinum* when the toxin and fat or oil are emulsified and injected subcutaneously into guinea-pigs. This protection is very limited and varies with the degree of the emulsion and the type of fat. The protection is due to a slowing down of the rate of absorption of the toxin.

15. Olive oil will delay the action of the toxin in the stomach of a rabbit when force fed immediately after the toxin and at repeated intervals. It apparently affords no greater protection than milk.

16. Certain food substances, such as glucose, brain tissue, milk, eggs and gelatin do not neutralize the toxin of *C. botulinum* and do not protect as effectively as olive oil against the action of the toxin in subcutaneous injections.

17. Apple vinegar, giving a positive test for alcohol, protects against the action of the toxin of *C. botulinum* when the two are mixed, incubated two hours and injected subcutaneously into guinea-pigs.

18. The protection afforded by the vinegar is not due to necrosis of the tissues, since vinegar neutralized with sodium hydroxid does not cause necrosis, and still protects against the action of the toxin. The protection afforded by the vinegar may be due to the alcohol present. Acetic acid and sodium acetate do not neutralize the toxin of *C. botulinum*.

19. Vinegar when force fed immediately after a toxin filtrate and at repeated intervals afforded some protection against the action of the toxin in the stomach of the rabbit.

20. Sodium hydroxid, potassium permanganate and liquid soap have a neutralizing action on the toxin of *C. botulinum*.

21. Epinephrin chlorid has a slight neutralizing action on the toxin of *C. botulinum*.

22. Iodin and iodin to which sufficient starch has been added to prevent necrosis of the tissues has a strong neutralizing action on the toxin of *C. botulinum*. Potassium iodid does not neutralize the toxin of *C. botulinum*. In "in vivo" experiments, iodin injected on the opposite side of the body from the toxin afforded no protection. Gram's solution affords some protection against the action of the toxin in the stomach of the rabbit when force fed immediately after the toxin.

SUMMARY

The treatment of botulism is in the experimental stage, and based mainly on insufficient or inexact knowledge. In experimental work with laboratory animals and in the treatment of human cases of botulism there has not been gained sufficient knowledge to develop a scientific treatment. This can be explained partly on the grounds that it is only within the past few years that the attention of the investigators has been drawn to the subject of botulism and partly to the fact that we are dealing with a powerful and rapidly acting toxin. However, we have reasons to believe that when further experimental work has been done, and physicians become better acquainted with the disease, a treatment will be developed that will materially lessen the death rate.

Specific Treatment.—The treatment of botulism may be classed as specific and general. By specific treatment we mean the use of an immune serum which neutralizes the specific toxin of *C. botulinum*. Since there are at least two distinct toxins, and there is no rapid means of determining the type, it is necessary to use a polyvalent antitoxin or a Type A and a Type B antitoxin. And since there is a possibility that *C. botulinum* occasionally produces its toxin in the body, the immune serum should be bacteriolytic or bactericidal as well as antitoxic. The serum should be injected intravenously.

The immune serum to be beneficial must be used as soon as possible after the diagnosis is made. In all cases of doubtful diagnosis, all of those having partaken of the suspected meal should receive immediate antitoxin treatment. The antitoxin can only neutralize the toxin and prevent further injury. It is of no value to the already damaged nervous system. The evidence we have indicates that treatment begun after the symptoms are well advanced will not, in most cases, alter the course of the disease. But we have sufficient experimental evidence to believe that some of those receiving lethal amounts of toxin can be saved by the use of antitoxin if the treatment is begun at about or before the time the symptoms appear.

General Treatment.—The general treatment of botulism consists of treatment of the digestive tract and stimulation of the nervous system.

Botulinus toxin is a true toxin and differs from the toxins of diphtheria and tetanus in that it is, so far as we know, taken into and possibly produced in the digestive tract and is not altered by the gastric juice. This gives us an opportunity to develop a treatment directed against the toxin in the digestive tract as well as in the blood stream.

Treatment of the digestive tract in cases of botulism has been designed to prevent the further absorption of the toxin by its removal, stimulation of gastric secretions, the use of demulcents and oils. A method of neutralizing the toxin in the digestive tract should also be developed.

Intestinal Tract: Treatment of the intestinal tract in cases of botulism cannot be placed on a scientific basis until we know the effect of the intestinal contents on the toxin. Graham has shown that the droppings of chickens suffering from botulism and also droppings found in forage causing botulism when ground up and fed to horses caused death. He apparently assumes that the toxin passed through the intestinal tract of the chickens and that the horses died as the result of the ingestion of this toxin rather than from the production of toxin in the digestive tract following the ingestion of toxin-free organisms. Forssman has shown that the injection of 2,000 lethal doses of toxin in the rabbit intestine does not cause death. He believed that the intestinal contents of the rabbit precipitated the toxin. Until we know whether or not the toxin in the intestinal tract is harmful we must proceed upon the assumption that it is and take steps for its removal, neutralization and the prevention of absorption.

We recommend the use of high enemas that will neutralize the toxin, prevent its absorption and destroy the organisms. We have shown that some of the common ingredients of enemas should be beneficial. Liquid soap neutralizes the toxin, olive oil prevents its absorption and turpentine may have some beneficial action. Iodin and potassium permanganate destroy both the toxin and organisms and might be used to advantage. The effect of soap on the organism is unknown and should be determined. If it can be shown that the toxin in the intestinal tract is harmless and is not produced there, the use of enemas can be restricted to feeding and the control of constipation.

Stomach: In those patients in which the symptoms do not appear for several days after the ingestion of the toxic food, we may reasonably assume that there is very little, if any, of the ingested toxin remaining in the digestive tract. But since there is a possibility of infection and production of toxin in the digestive tract, it is necessary to proceed on the assumption that toxin is always present in the stomach of any one suffering from botulism. When the symptoms appear in a

few hours after the ingestion of the poisonous food we should expect to find toxin in the stomach. In these cases paralysis of the stomach apparently sets in early. Case reports show that toxin has been found in the stomach several days after the ingestion of the toxic food.

Treatment of the stomach should have in mind the removal of the toxic contents by stimulation of movement or the stomach pump, the prevention of absorption by the use of demulcents and oils or stimulation of secretions, the neutralization of the toxin and the destruction of the organisms. The removal of the stomach contents is attended with some danger as it may induce pneumonia. The death rate among those vomiting is 75 per cent.; among those not vomiting, 70 per cent. The average time of death of those vomiting is 3.7 days and of those not vomiting 5 days after the ingestion of the toxic food. This indicates that those ingesting the most toxin tend to vomit or the act of vomiting induces a terminal pneumonia.

In our experimental work we have shown that the food taken in with the toxin delays the appearance of the symptoms. This is probably due to a slowing down of the rate of absorption of the toxin. Our work has also shown that a slowing down of the rate of absorption enables a guinea-pig to resist 3 lethal doses of toxin. The use of oils, milk and alcohol slowed down the action of the toxin in the stomach of the rabbit. Iodin, potassium permanganate and liquid soap have a strong neutralizing action on the toxin but it has not been determined whether they can safely be used in the stomach in large enough amounts to be beneficial.

Treatment of the stomach must be begun early, as paralysis of the throat soon sets in and there is great danger of pneumonia. Most of our rabbits dying after the fourth day showed gray hepatization of the lungs. A nonirritating gargle of 2 per cent. argyrol may be used as a precautionary measure.

Throat: Pilocarpin has been used to remove the tenacious mucus usually found in the throat in advanced cases. It "should be used with caution as the patient is unable to cough up fluid from the lungs if pulmonary edema is induced."

Nervous system: Treatment of the nervous system must be general until we know what nerves or nerve centers are affected. Strychnin has been used in most cases.

Supportive measures: The supportive measures in use have been mentioned above.

We cannot hope for a more satisfactory treatment until our knowledge of the subject becomes more exact. With our present knowledge of botulism, the death rate should be reduced when antitoxin becomes more available and the symptoms more readily recognized.

PROGNOSIS

From an examination of the incomplete statistical data we obtain certain facts which have a bearing on the prognosis. The death rate in this country varies from 60 to 70 per cent. The death rate among those first showing symptoms in all outbreaks in this country is 90 per cent., among those last showing symptoms 60 per cent. The death rate of those vomiting is 75 per cent. Vomiting cannot be considered a favorable sign. The death rate of those showing symptoms in twenty-four hours after the ingestion of the toxic food is 84 per cent.; of those showing symptoms for the first time after seventy-two hours it is 55 per cent., and of those alive after the eighth day it is 20 per cent.

THE RELATION OF HYPERTHYROIDISM TO DIABETES MELLITUS*

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At a meeting of the Deutscher Kongress für innere Medizin in 1906, Friedrich Müller [1] suggested that a special type of glycosuria is related to exophthalmic goiter. His immediate reasons for this belief were drawn from his experience with two cases. The first was one of exophthalmic goiter in which he had given thyroidin, hoping thereby to diminish the size of the thyroid gland. The symptoms of hyperthyroidism did not improve under this form of treatment and sugar began to appear in the urine in increasing amounts. The glycosuria did not diminish after administration of the thyroidin was stopped, and the patient died in coma a few months later. The second case was that of a woman with a chronic goiter who had taken thyroid extract for a long time, and who had developed diabetes. Some time later the goiter disappeared spontaneously, and, to Miller's surprise, the symptoms of diabetes also disappeared so that the patient was eventually able to take large amounts of carbohydrate without producing glycosuria. These two cases were the basis for Müller's statement that, in the future, the thyroid gland should be studied more carefully in its relation to diabetes.

Since the publication of Müller's paper on this subject, numerous others have appeared in European literature, although but little attention has been paid to it in this country. My purpose is to discuss this topic and to present such data as I have been able to collect from the records of the Massachusetts General Hospital and from the Mayo Clinic.

The earliest report on the relation of the thyroid gland to diabetes was read by Dumontpallier [2] of Paris at a meeting of the Societé de Biologie in August, 1867. It is of sufficient historic interest in connection with my paper to deserve a translation:

EXOPHTHALMIC GOITER AND GLYCOSURIA IN THE SAME PATIENT

A woman, aged 22, complained, according to her family, of chest trouble. Careful examination, however, demonstrated that the lungs were not seriously diseased. The patient was very pale and thin; her eyes were abnormally

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* From the Massachusetts General Hospital, Boston, and the Mayo Clinic.
* Presented before the Chicago Society of Internal Medicine, Chicago, November, 1920.

1. Müller, F.: Discussion, Verhandl. d. Cong. f. inn. Med. **23**:100, 1906.
2. Dumontpallier: Goitre exophthalmique et glycosurie chéz la même malade, Compt. rend. Soc. de biol. **4**:116, 1867.

prominent, and her expression was peculiar. The thyroid gland was hypertrophied, especially in the right lobe, and the patient complained of marked pulsation in her heart. The case was undoubtedly one of Basedow's disease, and the condition had been more marked at an earlier date.

Boulimia and excessive thirst had been persistent for several months. The presence of diabetes was suspected, and the urine was examined by Dr. Hardy of Paris, who demonstrated the presence of 62 gm. glucose to the liter of urine. The patient could not accurately estimate the volume of urine excreted in twenty-four hours, but it was considerable, and at night she was often awakened by a desire to urinate.

The prognosis was grave, not on account of the exophthalmic goiter, which is a curable disease and one compatible with life, but on account of the glycosuria which had caused the anemia and great loss of weight.

The patient followed the prescribed treatment for several weeks and showed considerable improvement. Her strength returned; her urine became less abundant, and there was no remission of the Basedow's disease. However, she caught a severe cold in the winter of 1867 and died of an inflammation of the chest.

The existence of these two nervous disorders in the same individual and the development of their principal symptoms is recorded for the benefit of all medicine.

We should add that the etiology in this case is of no less interest than the course of the disease. This young girl developed the first symptoms of exophthalmic goiter a few days after the suppression of her menstruation. The circumstances were as follows: The young woman became overheated at a fête, plunged her arms into a basin of cold spring water and sat down on the damp grass in the shade. The menstruation was stopped by this imprudence and never returned.

These words, twenty-seven years after Basedow's [3] original monograph was published, and seventeen years after Fehling's quantitative method for sugar determination in urine was described,[4] are the first note with regard to this unusual combination of diseases. The first case which appeared in English literature was that of Lauder Brunton [5] in 1874. Hartmann [6] reported two cases from the Tübingen Clinic in 1878. Budde [7] reported two cases in Denmark in 1891, and finally Manges [8] of New York, in 1899, recorded the first case in America. The early papers on this group of cases emphasized the association between two uncommon conditions and did not make any serious effort to inquire into their possible relationship.

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3. Basedow, v. C.: Exophthalmos durch Hypertrophie des Zellgewebes in der Augenhöhle, Wchnschr. f. d. ges Heilk. **6**:197, 1840.

4. Fehling, H.: Ueber die quantitative Bestimmung von Zucker und Starkemehl mittelst Kuppervitriol, Ann. Chem. et Pharm. **72**:106 1849.

5. Brunton, L.: Cases of Exophthalmic Goiter, St. Barth. Hosp. Rep. **10**: 255, 1874.

6. Hartmann, C.: Ueber zwei mit Basedow'scher Krankheit complizirte Fälle von Diabetes mellitus, Inaug. Diss. Tübingen, Fues, 1878.

7. Budde, V.: Ugesk. f. Læger **22**:1890. Review in Neurol. Centralbl. **10**:112, 1891.

8. Manges, M.: A Case of Exophthalmic Goiter with Diabetes Mellitus and Pigmentation, Mt. Sinai Hosp. Rep. **2**:59, 1899.

In 1909 Sattler [9] made a more elaborate study of the subject. He collected fifty-six reported cases, thirty-seven of which had been followed for a time sufficient to afford positive information. Twenty-five of these ended fatally in a comparatively short time; seven patients died in coma. In the majority of cases the diabetes developed after a pre-existent exophthalmic goiter, although in a few the diabetes seemed to antedate the thyroid disturbance. There seemed to be a certain hereditary influence in several so that Sattler commented on the frequency with which one or the other disease occurred in various members of the same family. None received surgical treatment.

Recently, more and more speculation as to the reason for the coincidence between these diseases has developed. Certain observers believe that it is purely by chance that the two are found together. Others argue that since thyroid extract can produce alimentary glycosuria in various normal persons and can exaggerate an alimentary glycosuria in almost all persons with hyperthyroidism, the relationship between diabetes and hyperthyroidism is closer. Finally Falta,[10] by fathering the school of endocrinologists, stimulated an immense amount of clinical and experimental work on the interrelationship of the various ductless glands.

It is not my purpose to attempt to analyze the evidence in favor of and against the interdependence of the thyroid, the pancreas and the suprarenals in diabetes and hyperthyroidism. The fact remains that the two diseases occur together at times, whether by chance, or because over-activity of the thyroid stimulates metabolism and eventually fatigues the pancreas until diabetes develops in predisposed persons, or through a physicochemic reaction between the internal secretions of the thyroid and pancreas.

Suggestions have been made that the peculiar characteristics of the thyroid gland may be used for therapeutic purposes in the management of diabetes. Falta [11] reported three cases of exophthalmic goiter and diabetes in which the patients were treated by roentgen-ray exposure of the thyroid gland. Two patients derived no apparent effect. The third patient, who excreted about 15 gm. dextrose after a diet containing 80 gm. carbohydrate, appeared to improve after one roentgen-ray treatment. The urine cleared up and remained sugar-free, even when a more liberal diet was eaten; the patient gained weight and the symptoms of thyroid tumor and diabetes disappeared so that the man

9. Sattler: Die Basedow'sche Krankheit, Leipzig, Engelmann **1**:384, 1909.
10. Falta, W.: The Ductless Glandular Diseases, Philadelphia, Blakiston, 1916, pp. 674.
11. Falta, W.: Ueber Glykosurie und Fettstühle bei Morbus Basedowii; zugleich ein Beitrag zur Röntgentherapie dieser Krankheit, Ztschr. f. klin. Med. **71**:1-22, 1910.

was considered normal when he was discharged from the hospital. Crile [12] operated on a man, aged 42, with diabetes whose urinary sugar averaged 95 gm. each day before operation. The left and right cervical sympathetic nerves were resected, the left suprarenal was removed and a partial thyroidectomy performed. Four months later the patient had gained 9 pounds in weight and was remaining aglycosuric on a diet containing 250 gm. carbohydrate. O'Day [13] treated four patients with exophthalmic goiter and diabetes. The first was a man, aged 24, who was thyroidectomized after preliminary hot water injections into the gland substance. His recovery was surprisingly rapid and within a short time his diet was unrestricted and his urine remained sugar-free, even when he ate candy. O'Day's other patients were handled in similar manner and recovered a practically normal carbohydrate tolerance. Rhodenburg's [14] two observations are nearly identical. He described one interesting case in which the father, mother, and one maternal aunt were diabetic, the patient himself developing the disease at the age of 18. The four members of the family were given thyroid extract at intervals which repeatedly caused a marked increase in sugar excretion in all. Finally, the man in question developed symptoms suggesting exophthalmic goiter and a portion of his thyroid gland was removed. About six months after the operation his urine was sugar-free, even after three ice cream sodas taken within twelve hours. Rhodenburg's second case was that of a woman, aged 53, who developed symptoms of excessive thyroid activity in 1915 and diabetes in 1919. Three months after thyroidectomy she had gained 35 pounds and her urine remained sugar-free with an unrestricted diet.

On the whole, so far as may be judged from the literature, a possible relationship between hyperthyroidism and diabetes has been recognized for a long time. The combination is relatively uncommon but is serious. Many theories as to the cause of such intimate association between these two diseases of metabolism have been brought forward, although at present the evidence is so conflicting as to be inconclusive. Attempts have been made to treat diabetes through the thyroid gland, and a few cases have been reported in which, when the thyroid tumor disappeared, either spontaneously, by roentgen-ray exposure, or by operative interference, the diabetes improved in striking fashion and possibly was cured.

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12. Crile, G. W.: The Kinetic Drive; Its Phenomena and Its Control, J. A. M. A. **65**:2129 (Dec. 18) 1915.

13. O'Day, J. C.: Carbohydrate Tolerance in Hyperthyroidism, Surg., Gynec. & Obst. **22**:206, 1916. Diabetes in Association with Toxic Goiter, New York M. J. **111**:815, 1920.

14. Rohdenburg, G. L.: Thyroid Diabetes, Endocrinology **4**:63, 1920.

The material presented in this paper consists of thirty-nine hitherto unreported cases of diabetes complicated by thyroid disease. Thirty-three of the patients were observed in the Mayo Clinic and six in the Massachusetts General Hospital. A number of cases of thyroid disease and mild glycosuria were observed in both institutions but were excluded from this series on the ground that the relation between transitory glycosuria in thyroid disease and true diabetes has not been established.

The combination of exophthalmic goiter and diabetes is no more common in America than in Europe. Billings [15] found one case of glycosuria in a series of sixty-one cases of exophthalmic goiter in Chicago; Greeley [16] found six cases of exophthalmic goiter in 614 cases of diabetes at Waukesha, and in the Mayo Clinic records there were only nine cases of diabetes among the 1,800 cases of exophthalmic goiter which were reviewed for this paper. Possibly these two diseases occur together more frequently along the eastern sea border than in the Middle West, since Thompson [17] reported three cases of diabetes among eighty cases of exophthalmic goiter in New York and there were four diabetic patients among 315 with exophthalmic goiter and hyperthyroidism at the Massachusetts General Hospitall.

A statistical review of the cases in this series does not add anything to Sattler's work. The age, sex and type of cases were much the same as his. Three of the four nonoperated patients with thyroid toxemia whose histories were followed for a reasonable length of time died within a few months after the diabetes was first apparent. Of the twenty-two cases, including hyperthyroidism due to exophthalmic goiter and adenoma, only one was known to be diabetic before the thyroid symptoms supervened, although in a few, as in Sattler's series, it was impossible to differentiate the symptoms of the two diseases. An hereditary influence was suggested in two cases; one patient's mother died of diabetes and another patient's mother and brother died of diabetes.

The main interest in the cases of this series lies in the fact that they made it possible to follow the effect of thyroid operations on the course of diabetes in a few more cases than had been published. Only those cases are included for this study which were followed until death or long enough to avoid apparent immediate results which were not true. The material is tabulated in Tables 1, 2, 3 and 4.

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15. Billings, F.: Symposium on Exophthalmic Goiter, J. A. M. A. **48**:349 (Jan. 26) 1907.

16. Greeley, H. P.: Focal Infections and Their Relation to Diabetes, Wisconsin M. J. **14**:464, 1915.

17. Thompson, W. G.: Exophthalmic Goiter. A Clinical Study of Eighty Cases, Tr. Assn. Am. Phys. **21**:502 1906.

In Table 1 are tabulated the findings in five cases of diabetes associated with nontoxic thyroid enlargement. These cases seem fairly representative of ordinary diabetes. Three patients died in typical fashion, one of pulmonary tuberculosis, one after a surgical operation

TABLE 1.—Nontoxic Thyroid Disease and Diabetes — Nonoperated Cases

Case, Age, Sex	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Remarks
			Per Cent.	24-Hr. Amount Sugar, Gm.				
1 51, M	2 yrs.	18 mos.	6.0	224	220	102	1/ 5/10 1/31/14	Died of diabetes
2 32, F	10 yrs.	2 mos.	6.0	102	100	95	5/29/17 1/13/19	Losing weight and strength rapidly despite treatment*
3 67, F	Since a girl	Not known	2.5-7.0	—	—	—	10/ 7/14	Died shortly after operation for cancer of the uterus
4 49, F	25 yrs.	7 yrs.	3.0	36 none	170	170 161	6/15/18 8/ 2/20	B.M.R.—17 B.M.R.—9; has been dieting carefully since last entry
5 47, M	13 yrs	4 yrs.	—	450	—	—	4/ 3/11 5/ 3/11	Death; necropsy showed pulmonary tuberculosis

* Patient died June 5, 1918.

TABLE 2.—Nontoxic Thyroid Disease and Diabetes — Operated Cases

Case, Age, Sex	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Remarks
			Per Cent.	24-Hr. Amount Sugar, Gm.				
1 57, F	Since a child	Not recorded	4.0	80	150	115	8/25/19 9/12/19 3/22/20	Partial thyroidectomy Living on strict diet; keeps sugar free except for trace occasionally
2 32, F	22 yrs.	8 mos.	5.0 3.0	170 140	200 ...	148 ...	5/15/19 5/31/19 3/22/20	Partial thyroidectomy Feels fairly well; diabetes unimproved
3 55, F	26 yrs.	Not recorded	7.0 1.2	84 ...	160 ...	152 150	5/ 5/15 8/ 8/15 3/15/20	Partial thyroidectomy Is restricting diet to best of ability; diabetes unimproved
4 54, F	30 yrs.	6 mos.	2.0 4.5	22 44	190 ...	182 180	7/22/19 8/13/10 3/18/20	Partial thyroidectomy Diabetes unimproved

on the uterus, and one, a man, aged 51, after six years' illness. One woman, (Case 2), aged 32, had a rather acute diabetes but there was no evidence for believing that the thyroid enlargement accelerated its course. Case 4 is the most interesting of this group. The patient had

diabetes with moderate hypothyroidism. The diminished metabolism did not increase the sugar tolerance because it was no lower when the metabolic rate was more nearly normal. These cases suggest that nontoxic thyroid disease does not affect diabetes.

In Table 2 are tabulated the findings in four cases similar to those described in Table 1. The patients were all elderly persons with mild diabetes. They had had partial thyroidectomies without cure of the diabetes, nor was it obviously affected. These cases, therefore, suggest that thyroidectomy alone is a valueless therapeutic measure in diabetes.

TABLE 3.—TOXIC THYROID DISEASE AND DIABETES—NONOPERATED CASES

Case, Age, Sex	Type of Goiter	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Remarks
				Per Cent.	24-Hr. Amount Sugar, Gm.				
1 40, F	Exophthalmic	8 mos.	2-3 mos.	4.0	—	115	102	11/18/16 11/28/16	Died suddenly; necropsy showed persistent thymus
2 19, F	Exophthalmic	1 yr.	Not present	—	—	—	129	1/ 1/09	
			Not present	—	—	—	123	4/20/11	Feeling fairly well; still has exophthalmic goiter
			4 mos.	—	450	—	87	10/ 8/12	Developed acute diabetes; running down hill rapidly; end result unknown
3 30, F	Exophthalmic	7 yrs.	2 mos.	— 3.6	161 —	— ..	— ..	7/ 9/14 9/29/15	Died of diabetes

In Table 3 are tabulated data from three cases of exophthalmic goiter complicated by diabetes, in which operations were not performed. This material is small but noteworthy. The three goiter cases are not unlike Dumontpallier's original case in the rapidity of their course. Case 2 is especially interesting since the patient did not develop diabetes until she had had a goiter for at least two years. Finally, the diabetes became extremely acute. These cases suggest that patients with exophthalmic goiter, because of their high metabolism, burn themselves up quickly if diabetes develops, although more detailed information on the relation of the metabolic rate to prognosis of the diabetes in the various types of goiter is highly desirable. In any event these cases of true exophthalmic goiter accompanied by diabetes emphasize the gravity of the condition.

Table 4 represents the results in nine cases of exophthalmic goiter and toxic adenoma in which operation was performed. These cases are all interesting individually. In Case 1 the patient did not have diabetes until after the thyroid vessels had been ligated. Although

TABLE 4.—Toxic Thyroid Disease and Diabetes — Operated Cases

Case, Age, Sex	Type of Goiter	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Glycosuria		Maximum Weight, Pounds	Present Weight, Pounds	Date	Operation and Remarks
				Per Cent.	24-Hr. Amount Sugar, Gm.				
1 41, M	Exophthalmic	2 yrs.	Not present	—	—	175	142	6/15/16 7/ 5/16 7/10/16 7/14/16	Hot water injection Ligation of thyroid vessels
			Acute onset	9.0	180	...	116	9/ 9/16 1/ 2/17	At first improvement after operation, then rapid downward course Death
2 33, M	Exophthalmic	3 mos.	Not recorded	Trace	Trace	130	115	10/12/15 10/16/15 10/21/15	Ligation of thyroid vessels
			No symptoms	2.0	...	...	119	12/14/15	Right lobe and isthmus extirpated
				None	None	...	115 124	9/ 8/16 10/ 4/16	Dieting strictly Had two roentgen-ray treatments
			3 mos.	2.0	54	...	101	6/29/18	Losing rapidly
3 37, F	Exophthalmic	9 yrs.	3 mos.	2.5	100	140	96	10/ 6/14 11/19/14 11/24/14 11/27/14	Ligation of thyroid vessel Right lobe, isthmus and part of left lobe extirpated Death
4 47, F	Exophthalmic	1.5 yrs.	Not recorded	2.0	87	165	122	1/30/14 2/12/14 2/17/14 2/12/19 12/22/19	Ligation of thyroid vessels Right lobe, isthmus and ¾ left lobe extirpated Dieting; sugar now in urine every day Died of diabetes and pneumonia
5 44, M	Exophthalmic	8 mos.	1 yr.	1.4	12	170	170	1/15/15 1/22/15 1/29/15	On strict diabetic diet Ligation of thyroid vessels
				1.0	—	...	177	5/ 8/15 5/14/15 3/15/20	Patient returned Extirpation of right lobe and isthmus Urine has no sugar; patient not dieting
6 57, F	Adenoma	7 yrs.	1 yr.	4.0	72	170	130 145 152	5/ 7/18 6/14/18 3/20/20 11/19/20	Partial thyroidectomy Not dieting; feeling well; no glycosuria Not dieting; feeling well; trace of sugar
7 53, F	Adenoma	40 yrs.	6 yrs.	4.0	80	180	154 165	10/12/17 11/20/17 3/20/20	Partial thyroidectomy Not dieting; feeling well; no glycosuria
8 52, F	Adenoma	Years	1.5 yrs.	4.0	80	170	140	3/ 8/16 5/20/16 6/ 4/19 11/16/20	Partial thyroidectomy* Tonsillectomy Has regained weight and strength; urine sugar free except when she overeats of starchy foods
9 58, F	Adenoma	40 yrs.	9 yrs.	3.0	30	160	136	9/ 5/19 10/ 1/19 10/ 5/19	Partial thyroidectomy Died of bronchopneumonia

* I am obliged to Dr. George Kessel of Cresco, Iowa, who performed the operations quoted in this case and who has given me the subsequent information.

the patient improved subjectively, the operation did not prevent the development of diabetes and the patient died after a short course. In Case 2, the patient had a trace of sugar on first observation, but no diabetic symptoms. However, his mother and one brother died of diabetes, so possibly there was an inherited tendency toward the disease. The treatment consisted in ligation of the thyroid vessels, partial thyroidectomy, strict diet, and roentgen-ray exposure of the thyroid remnant. Such thorough treatment did not affect the course of the diabetes. In Case 3 the patient, a woman, died immediately after operation. In Case 4, the patient had a ligation of the thyroid vessels; the right lobe, isthmus and five-sixths of the left lobe of the thyroid were extirpated. Moreover, the patient dieted strictly. In spite of this treatment she was still a diabetic when she died, although she lived for nearly six years after she was first examined and did not develop acute diabetes as in the other cases. In Case 5 the patient had the mildest type of diabetes of the series. He improved after operation and had no sugar on an unrestricted diet five years after he was first examined. This patient was a true diabetic and had been under treatment before he developed exophthalmic goiter. The superimposed thyroid toxemia did not seem to affect the diabetes especially; therefore, it is difficult to be convinced that the thyroid operation was the only cause of the apparent improvement in the diabetes. Cases 6, 7 and 8 are more suggestive of the cases described by O'Day and Rohdenburg. The patients had toxic adenoma and partial thyroidectomy on this account. The patient in Case 6 had gained 22 pounds two and one half years after operation, was feeling well, was not dieting, and the urine contained only a trace of sugar. The patient in Case 7 had almost an identical result from the operation. Two and one-half years later she had gained back twenty-two pounds of weight and was feeling well. The patient in Case 8, four and one half years after operation, was reported to have regained her weight and strength and to be aglycosuric most of the time. The patient in Case 9 developed bronchopneumonia after partial thyroidectomy and died.

On the whole, the results of operation on the thyroid gland of diabetic patients with hyperthyroidism in this small number of cases were not particularly encouraging. However, Cases 4, 5, 6 and 7 suggest that occasionally an operation may not only prolong life but may even be of greater benefit.

The series is too small to afford conclusive evidence with regard to the advisability of operation in this type of case. However five patients with nontoxic goiter were operated on with no mortality, six with toxic adenoma with one death, and six with exophthalmic goiter with one death. Therefore, it does not seem overradical to advise operation for properly selected and prepared patients in this group of cases, since

the risk does not seem out of proportion to the possible benefit to be gained, and since the prognosis is otherwise very grave.

Obviously my observations are too fragmentary to warrant any definite conclusions and I can only draw attention to certain features with regard to the relationship between thyroid disease and diabetes.

Hyperthyroidism and diabetes occur together in the same person in a small number of cases. There is no established evidence that such coincidence is more than chance.

The diabetes usually follows the thyroid disturbance, but may precede it, and tends to parallel in severity the severity of the thyroid intoxication.

There is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes as the patients in this series with nontoxic goiter who were operated on showed no improvement of the diabetes.

Certain patients with toxic thyroid disease and diabetes, on the other hand, improve to a considerable degree after the thyroid symptoms are checked. This probably occurs because of a change in the rate of metabolism and not because a portion of the thyroid gland has been made functionless. Before this supposition can be established more accurate information must be obtained with regard to the effect of an increased rate of total metabolism from thyroid intoxication on the carbohydrate metabolism of diabetics.

THE OCCURRENCE OF ABNORMAL LEUKOCYTES IN THE BLOOD IN ACUTE INFECTIONS

ACUTE BENIGN LYMPHOBLASTOSIS

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During the past year we have had several acute infectious cases, running a febrile course, usually mild and all ending in recovery, but in which the blood picture gave rise to considerable apprehension, at the time, as to the ultimate outcome.

The appearance in the blood of cells indistinguishable from those found in acute leukemia, together with enlargement of the lymph nodes and sometimes enlargement of the spleen, with a moderate fever, and absence of definite signs pointing to other disease entity, is a clinical picture that might easily give rise to a grave prognosis.

An excessive proportion of lymphocytes, a reversal of the polymorphonuclear lymphocyte relation, is not infrequently seen in the normal blood of children, and occasionally in adults under pathologic conditions other than lymphatic leukemia. A lymphocytosis is also noted in some cases following the administration of certain therapeutic agents. In early childhood is found the most marked increase, due to congenital syphilis, cholera infantum, rickets, scurvy and pertussis. In adult life, hemophilia, cervical adenitis, enlarged tonsils, chlorosis, pellagra, exophthalmic goiter, varicella, mumps, secondary anemia associated with syphilis, tuberculosis and malaria frequently show an excessive percentage of lymphocytes in the blood. This condition is also noted at times following the administration of therapeutic doses of thyroid extract, tuberculin, pilocarpin, and quinin hydrochlorate subcutaneously.

However, the cases presented in this series have a different aspect and clinical picture from the type of cases noted above. They also present a different picture from that found in acute leukemia, and while each new case may give rise to grave doubts as to prognosis, a careful investigation and study of the history and findings will usually serve to distinguish this type of case from true leukemia.

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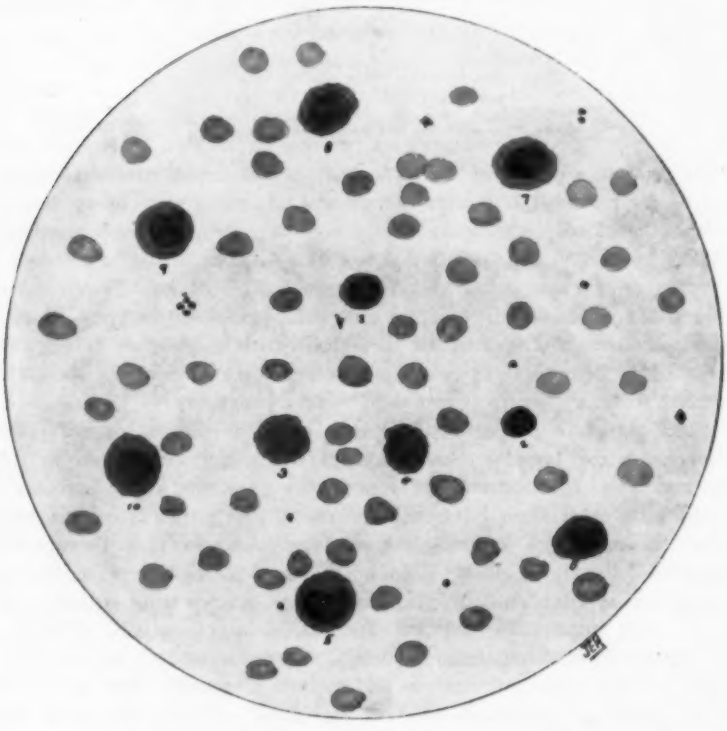
* From the Division of Clinical Medicine of the U. S. Naval Hospital.

Whether or not these cases represent a distinct disease entity may, perhaps, be questioned, but the term "acute benign lymphoblastosis" is suggested as covering the essential features of this disease.

The symptoms, physical findings and course of the disease, in themselves, are not alarming, but when viewed in conjunction with the blood findings the case presents a rather distinct and often startling picture.



Composite blood picture drawn to show type of lymphoblast encountered in "acute benign lymphoblastosis." 1 and 2, large and small lymphocyte commonly seen in normal blood; 3, large mononuclear cell (endotheliocyte); 4, polymorphonuclear neutrophil; 5, 6, 7, 8 and 9, types of lymphoblasts encountered in "acute benign lymphoblastosis," rarely seen in normal blood; 10, Rieder type of lymphoblast.

REPORT OF CASES

Case 1.—White male; aged 19; unmarried.

Complaint.—Cough, general malaise, soreness in upper respiratory passages.

Family History.—Negative.

Personal History.—Smallpox and measles in childhood; influenza in 1918, duration two weeks, good recovery; occasional attacks of tonsillitis during past five years.

Present Illness.—The patient had been feeling badly for about one week prior to admission to hospital. He had headaches, slight cough and lassitude.

Physical Examination.—On admission, temperature, 103.8 F.; pulse, 104; respiration, 22. The patient was well nourished, with a fair amount of subcutaneous fat. The color of the skin and mucous membranes was good; no petechiae. Glands in neck, anterior, posterior and submaxillary, were enlarged, as were those in the axillae and groins. They were discrete and mobile. Those in the groin were particularly prominent, filling Scarpa's triangle and extending upward along Poupart's ligament nearly to the anterior superior spine. Pupils were equal and reacted to light and accommodation. Tongue thick, red and somewhat velvety. Tonsils were large and there was some angina; pharynx moderately congested; teeth extensively filled, but otherwise good. There was a faint systolic murmur at left second interspace, otherwise heart was negative. Lungs showed a few scattered râles, inconstant in distribution.

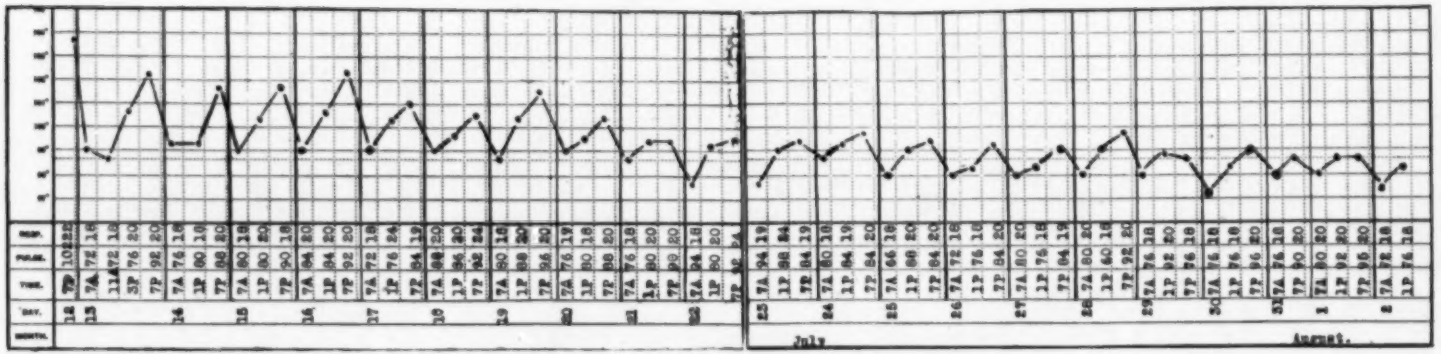
TABLE 1.—Blood Chart of Case 1

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myeloeytes, %	Rieder Type Lymphoblast, %	Unclassified Leukocytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
7/18	30,000	15	84	0	0	0	0	1	0	0	4,200,000	78	
7/19	34,000	12	87	0	0	0	0	0.5	0	0.5	.....	..	Rieder cell (?)
7/22	24,000	8	89	0	0	0	0	3	0	0	.....	..	Widal negative
7/26	14,000	14	84	0	0	0	0	1	0	2	.....	..	Blood culture neg.
7/29	11,200	13	86	0	0	1	0	1	?	0	.....	..	Throat smear: fusospirillary (Vincent's) organisms
8/ 2	9,500	10	86	0	0	3	1	0	?	0			
8/ 5	7,800	30	69	0	0	1	0	0	0	0	.....	..	Wassermann neg.
8/12	7,500	37	58	0.5	0	3.5	0.5	0	0.5	0.5	.....	..	Rieder cells
8/18	6,200	34	58	0	0	6	0.5	0	0	0.5	.....	..	Coagulation time, 4 minutes
8/23	9,000	35	57	1	0	6.5	0.5	0	0.5	0	4,400,000	85	Feces negative for ova and parasites
9/ 4	5,500	38	55	1	2	4	0	0	0	0			
9/29	6,200	63	34	0.5	0.5	2	0	0	0	0	4,880,000	95	No abnormal cells seen
12/ 2	7,100	57	39	0.5	0.5	2	1	0	0	0	5,400,000	100	

Abdomen appeared to be full and tense; liver not enlarged; spleen not palpable but appeared enlarged to percussion; no tenderness; no tumors. Bones of limbs showed no swelling or tender areas. Reflexes, both superficial and deep, were normal. Eye grounds negative.

Laboratory Data.—Urine showed a trace of albumin and an occasional hyalin cast. Sputum showed no tubercle bacilli. Numerous streptococci, fusiform bacilli and spirillae were present in sputum. Throat cultures negative for Klebs-Loeffler bacilli. Smears from the throat showed the presence of Vincent's organisms during the acute stage of the disease. The blood was negative for malarial parasites and repeated blood cultures during the course of the disease were negative. The Noguchi reaction was negative. The Widal test was negative. Stools normal and negative for ova or parasites. The coagulation time of the blood was four minutes. The complete record of the blood examinations is shown in Table 1.

The character of the blood picture and the type of cell present were fairly constant in all the cases and will be described later in the report.



Pulse, respiration and temperature record in Case 1.

Clinical Course.—Patient continued to run a febrile course, temperature varying from 99 F. in the morning to 102 F. in the evening during the first week. During the second week the temperature gradually approximated normal and the patient was up and about at the end of the second week. The type of temperature chart in all these cases was very similar and usually after running a more or less continuous course for three or four days the fever became remittant, gradually approaching normal but with the tendency to slight evening rise during the second week. A section of the temperature chart in Case 1 is reproduced as being fairly characteristic of this disease. On the fifth day, the patient developed a superficial ulcer about the right nares which healed after ten days. The glandular enlargement gradually subsided. Six weeks following admission, the glands were still slightly enlarged but discrete and mobile. The increase in the lymphocytic cells persisted for several weeks after the temperature was normal and after the patient was free from all symptoms. Recovery was uneventful and patient has been pursuing his usual duties since discharge from hospital.

CASE 2.—White male; aged 20; unmarried.

Complaint.—Sore throat, swelling of glands of neck, and general malaise.

Family History.—Negative.

Personal History.—Measles, whooping cough and chickenpox in childhood. Occasional attacks of tonsillitis for past three years.

TABLE 2.—BLOOD CHART OF CASE 2

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lymphoblast, %	Unclassified Leukocytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
10/18	9,100	26	71	1	2	0	0	0	0	0	4,700,000	90	Throat culture negative for Kloebs-Loeffler bacilli
10/19	12,600	19	70.5	0	0	0	0	0	0.5	0	.....	..	Throat smears: fuso-spirillary (Vincent's) organisms
10/20	11,400	32	67	0.5	0	0.5	0	0	0	0			
10/21	9,800	43.5	56	0	0.5	1	0	0	0	0			
10/22	7,200	29	69	0.5	0.5	0.5	0	0.5	0	0			
10/24	7,100	51	48	0	1	0	0	0	0	0			
10/25	7,200	38	59	1	1	0.5	0	0	0.5	0	.....	..	Rieder cell
10/27	6,400	49	50	0	0	1	0	0	0	0			
10/29	7,600	64	32	2	0	2	0	0	0	0			
12/ 1	7,000	71	25	2	0.5	0.5	0	0	0	0	5,200,000	100	

Present Illness.—Patient has had headaches and throat has been sore for about one week. During this period he noticed swelling in glands of neck, which gradually increased up to the time of his admission to hospital.

Physical Examination.—On admission, temperature, 99 F.; pulse, 82; respiration, 20. Patient was well nourished and muscular. The color of the skin and mucous membranes was normal. There were no hemorrhagic areas. The glands of the neck, anterior, posterior and submaxillary, were greatly enlarged, so that the patient had difficulty in wearing collar. There was practically no tenderness and glands were not adherent or matted together. The glands in the groins and axillae were slightly enlarged. The epitrochlears were not palpable. Pupils were equal and reacted normally. Tonsils were hypertrophied and rather marked angina was present. There was a small ulcer over left tonsil covered with a grayish exudate. Teeth negative. Reflexes, both super-

ficial and deep, were normal. Lungs were clear and heart negative. Spleen not palpable and not enlarged to percussion.

Laboratory Data.—Throat cultures were negative for Klebs-Loeffler bacilli. Roentgenogram of chest showed hila shadows somewhat enlarged, more so on the right; bronchial trunks slightly more prominent than normal. No evidence of tuberculosis. Urinalysis negative. Smears from throat showed the presence of the organism of Vincent's angina. Blood negative for malarial parasites and blood cultures taken at various times during the course of the disease were negative. Stools negative for ova or parasites. The complete record of the blood examinations is shown in Table 2.

Clinical Course.—Patient ran a mild febrile course with tendency to evening elevation to 99.6 F. The angina gradually subsided and the glandular enlargement slowly disappeared. At the end of the twelfth day temperature remained normal and patient was up and about. Recovery was uneventful. Two months following discharge the glands of neck were still palpable but there was no visible enlargement of the neck. Glands of the groins and axillae normal. The blood picture in this case, as in the others of this series, showed a tendency to return to normal more slowly than the temperature, and abnormal cells could be found in the smears after patient was clinically well. The marked enlargement of the cervical lymph glands in this case raised the question of Hodgkin's disease, which, however, could be definitely ruled

TABLE 3.—BLOOD CHART OF CASE 3

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lymphoblast, %	Unclassified Leukocytes, %	Erythrocytes, per C.Mm.	Hemoglobin, %	Remarks
11/2	20,100	24	74	0	0	0	1	0	0.5	0.5	.....	..	Throat culture negative for Kloebs-Loeffler bacilli
11/3	20,200	22	76	1	1	0	0	0	0	0	.....	..	Throat smears: fuso-spirillary (Vincent's) organisms
11/8	14,600	38	60	0.5	1	1.5	0	0	1	0			
12/2	7,000	38	54.5	2	3	3	0.5	0	0.5	0	4,600,000	95	Rieder cell

out by the character of the enlargement, the blood picture and the clinical course. Since discharge from hospital patient has been pursuing his usual duties and feels entirely well.

CASE 3.—White male; aged 20; unmarried.

Complaint.—Sore throat, headaches and general malaise.

Family History.—Negative.

Personal History.—Mumps and tonsillitis in childhood; influenza in 1917, incapacitated one week, good recovery; furunculosis in 1918, duration ten days, no recurrence since; otitis media in October, 1920, which subsided in one week.

Present Illness.—Began rather suddenly with sore throat, loss of appetite, and feeling of lassitude. These symptoms gradually became more marked up to time patient was admitted to hospital.

Physical Examination.—On admission, temperature, 103.4 F.; pulse, 96; respiration, 22. Patient was well nourished and muscular. Skin and mucous membranes normal. No hemorrhagic areas. Glands in neck, both anterior and posterior, slightly enlarged and tender. Glands of axillae and groin not

enlarged. Tonsils hypertrophied and covered with follicular exudate. Pupils are equal and react normally. Heart and lungs negative. Abdomen slightly distended; no tender areas; no evidence of tumors. Spleen not palpable but enlarged to percussion. Liver not enlarged. Reflexes, both superficial and deep, are normal. Eye grounds negative.

Laboratory Data.—Throat cultures negative for Klebs-Loeffler bacilli. Smears from throat show presence of organisms of Vincent's angina. Blood was negative for malarial parasites and blood cultures all negative. The Noguchi reaction was negative. Stools normal and negative for ova and parasites. The sputum was negative for tubercle bacilli. Urine showed slight traces of albumin, otherwise negative. The complete record of the blood examinations is shown in Table 3.

Clinical Course.—Patient ran a continuous temperature for four days, following which the temperature became remittent, being normal in the morning and approximating 100 F. in the evening. At the end of the thirteenth day, the temperature remained normal, and the patient felt entirely well. The angina gradually subsided but the glandular enlargement of the neck persisted for several weeks. Recovery was uneventful, and the patient has been pursuing his usual duties since discharge from hospital and feels entirely well.

TABLE 4.—Blood Chart of Case 4

Date, 1920	Leukocytes, per C.Mm.	Polymorphonuclear neutrophils, %	Lymphocytes (all sizes), %	Mononuclears, %	Transitionals, %	Eosinophils, %	Mast Cells, %	Myelocytes, %	Rieder Type Lymphoblast, %	Unclassified Leukocytes, %	Erythrocytes, per C.Mm.	Hemoblobin, %	Remarks
11/6	6,000	46	51	0	2	0	0.5	0	0.5	0			
11/7	6,200	51	48	1	0	0	0	0	0	0			
11/9	6,400	43	53	3	2	1	1	0	0	0			
12/6	7,200	58	39	2	1.5	1.5	2	0	0	1	5,330,000	100	

Case 4.—White male; aged 19; unmarried.

Complaint.—Headache, general malaise and acute coryza.

Family History.—Negative.

Personal History.—Measles and mumps in childhood; acute enteritis in December, 1919; good recovery.

Present Illness.—About four days prior to admission patient had been having rather severe headaches and coryza, which gradually increased in intensity up to time of admission to hospital.

Physical Examination.—On admission, temperature, 100.6 F.; pulse, 84; respiration, 20. Patient was well nourished and showed no evidence of recent loss of weight. Color of skin and mucous membranes was normal and there were no hemorrhagic spots. Glands of neck showed slight enlargement but no tenderness; glands of groins and axillae not enlarged. Pupils are equal and react normally. Reflexes, both superficial and deep, are normal. Lungs show a few scattered râles more marked at both bases. Patient has an acute coryza with a rather free mucopurulent discharge from the nose. Heart negative; abdomen slightly distended and somewhat tender in lower left quadrant. There was evidence of accumulation of feces in sigmoid and descending colon; spleen was not palpable; liver not enlarged.

Laboratory Data.—Cultures from throat were negative for Klebs-Loeffler bacilli. Blood negative for malarial parasites and blood cultures all negative. Stools show no ova or parasites. Sputum negative for tubercle bacilli. Urine negative. Roentgenogram of chest entirely negative. The complete record of blood examinations is shown in Table 4.

Clinical Course.—Patient ran a continuous temperature for five days following which temperature became remittent and remained normal after ninth day. The abdominal tenderness disappeared following a copious enema. The blood picture gradually approximated normal and one month following discharge no abnormal cells were found. Recovery was uneventful and patient has been pursuing his usual duties since discharge from hospital and feels entirely well.

DISCUSSION

The blood picture is essentially the same in all of these cases; the leukocytosis, when present, seemed to be due to an increase in the lymphadenoid cells. These pathologic lymphocytes differ from the cells seen in lymphatic leukemia, in that they do not show the poor staining reaction of the cytoplasm and nucleus seen in that condition. No degenerated cells were observed in this series such as are frequently found in the acute leukemias. The heavy staining nuclei of the lymphoblast in this disease may be placed centrally or eccentrically; it is often round, oval, or irregular in outline, showing deep indentations and occasionally showing the clover-leaf or bilobed Rieder type nucleus. Occasionally, azure granules were noted in the cytoplasm and vacuoles in the dark opaque blue were not infrequently noted. None of these cells showed an oxidase ferment, thus differing from those of myelocytic origin. They are evidently the result of stimulation of lymphadenoid tissue rather than of bone marrow.

In this group we find cells of a distinctly pathologic type corresponding to the germinal center type of lymphoblast. Every gradation in size, from small lymphocytes corresponding in size to the red cell, to a type of cell distinctly larger than the mononuclear-transitional variety, often three times the diameter of the red cells, were noted. No effort is made to differentiate between the large and small cells in making the differential count, as such attempt would be futile.

The small lymphocyte, as a rule, stained normally with Wright's and Wilson's stain, but the majority of cells making up this group consist of large lymphadenoid cells with a protoplasm so darkly stained that it is at first difficult to distinguish them from myelocytes. Indeed, in some cases when hints of a granular appearance are noted in the darkly stained cytoplasm, we find it impossible to be sure whether we are dealing with a large lymphocyte or a myelocyte, except by special staining methods.

These cells have been described by Engel as "mononuclear cells" and by Weil as "nongranular myelocytes." Weil describes the salient

points of these cells as follows: "They look like a myelocyte whose granules have fused into a smooth homogeneous band of color around the spherical or ovoid nucleus. The protoplasm is homogeneous and deeply stained. . . . In leukemia they are often counted as myelocytes or large lymphocytes by unpracticed observers." Turck has described them under the name "Reizungsformen," and Cabot has found them in the blood of malignant disease and pernicious anemia. We have observed them under similar pathological conditions. The differential diagnosis between the endothelial leukocytes, i. e., the mononuclear transitional type, and the large lymphoblast, is not difficult. The smears do not show the rich violet staining pachychromatic nucleus and the protoplasm gives a distinctly washed out, frosted-glass appearance in contrast to the deeply stained lymphoblast. Peroxidase granules are never present in lymphoblasts while a few are always present in endotheliocytes.

We have found the more satisfactory and uniform method of staining slide preparations to be that devised by Russell; i. e., immersing the slide for one minute in Wilson's or Wright's stain in Coplin jars to fix the film and then three to five minutes in another jar of distilled water containing enough of the stain to tinge the water, usually about five drops. The Hasting's counterstain is omitted.

Goodpasture's stain for differentiating myeloblasts from lymphoblasts is satisfactory and of considerable aid in making the differential count in these preparations. It gives a clear differentiation between the granular and nongranular leukocytes. The differential count is made from a polychrome-methylene blue stain and the Goodpasture stain, allowing for the eosinophils which are undifferentiated by the latter in the total averages.

There still exists considerable confusion regarding the classification of abnormal leukocytes and various hematologists have established a division of their own which in some cases is inclined to be cumbersome. It appears to us not desirable to attempt to subdivide these lymphatic cells. The term lymphoblast is considered preferable to mononuclear leukocyte in describing these cells, as they are nongranular and are apparently of lymphadenoid tissue origin.

Stitt's classification of pathologic leukocytes is considered to be most practical in classifying these cells. He describes this type of cell under the heading of pathologic large lymphocytes as follows: "These are, as a rule, much larger than normal large lymphocytes and show poorer staining of both nucleus and cytoplasm. The nuclei often show the appearance of division into two or more lobes, thus showing the characteristics of Rieder cells. They may be confused with large mononuclears but are considered to be derived from the germinal centers of

various lymphoid tissues. They are found in leukemic and pseudoleukemic conditions. They never show peroxidase granules. This characteristic, together with sharper outlining of the nucleus, differentiates the pathological lymphocytes (lymphoblasts) from myeloblasts."

These cases all occurred in young adults; each ran a febrile course and each showed enlargement of the lymphatic glands, which, in three of four cases, was quite marked. Enlargement of the spleen was noted in two of the cases. The type of temperature which appears to be characteristic has been commented on already. The frequency of angina is noteworthy in these cases, particularly the presence of the organisms of Vincent's angina noted in three of the cases. However, we had several cases of Vincent's angina in which the blood smears showed no lymphoblasts, so that it is quite evident that this is not the common finding with a Vincent's infection. The possibility that the infection gains entrance through the upper respiratory tract and particularly by way of the tonsils appears to be a reasonable hypothesis. There was no evidence of tuberculosis, lymphosarcoma, or Hodgkin's disease in this series.

The differentiation of this type of case from acute lymphatic leukemia may be particularly difficult. The absence of degenerated and fragile cells in the blood smears, the early return of the temperature to normal, the mild course, the absence of hemorrhagic spots and the absence of particularly high leukocyte counts are distinguishing features. Nevertheless the resemblance to leukemia has been so striking in some of the cases that eminent hematologists have considered it impossible to differentiate this condition on the blood smears alone.

It would appear that the reaction noted in these cases was due to some infectious agent gaining entrance through the upper respiratory passages and resulting in a stimulation of the lymphadenoid tissues with the production of these abnormal cells which, however, disappear in the course of a few weeks or months, leaving the patient in a practically normal condition.

Sprunt and Evans, of Johns Hopkins Hospital, report six cases which resemble our series very closely. They have used the term "infectious mononucleosis" in describing this type of case, and they comment upon the marked similarity of these cases to acute leukemia. All of their cases recovered and all ran a comparatively mild course.

Stitt, in referring to lymphoid pseudoleukemia, states "it is difficult to differentiate this condition from true lymphatic leukemia when aleukemic. The white count varies from 5,000 to 10,000 with about 75 per cent. of lymphocytes. The spleen is enlarged as well as the lymph-nodes and there is a tendency to hemorrhage in the later stages." How-

ever, in our series of cases, there was no tendency to hemorrhage, the leukocyte count in three of the four cases was much higher than 10,000 and the type of cell is distinctly different from that found in lymphoid pseudoleukemia.

The findings in these cases may be summarized as follows:

1. The disease occurred in young adults and as a rule followed an infection of the tonsils or upper respiratory passages.

2. Three of the four cases showed the presence of the organisms of Vincent's angina in throat smears during the acute course of the disease.

3. The blood picture in this type of case bears great similarity to that of acute lymphatic leukemia. However, the total white count never became so large that it could not be accounted for as the result of reaction to acute infection; there was no hemorrhagic tendency and no degenerated or fragile cells were noted in the smears.

4. The predominating type of cell was the lymphoblast and the Rieder type of lymphoblast was frequently noted.

5. All of these cases showed enlargement of the lymphatic glands, particularly the cervical and submaxillary glands.

6. They all pursued a benign course and ended in complete recovery.

7. The term "acute benign lymphoblastosis" is suggested as covering this type of case.

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FOCAL INFECTION AND SELECTIVE LOCALIZATION OF STREPTOCOCCI IN PYELONEPHRITIS *

STUDY I

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In most nonspecific urinary infections, either in the bladder or in the kidney, a gram-negative motile bacillus, believed to be the colon bacillus, is generally the predominating organism in the urine. Naturally, investigation and treatment have been directed against this organism, and patients with pyelonephritis are not considered cured until specimens catheterized from each kidney are found to be free from both bacteria and pus.

Recently, investigators have centered their attention on this organism. During the chill incident to the removal of residual urine in prostatic cases, colon bacilli have been recovered from the blood in as high as 40 per cent. of cases.[1]

Helmholz and Beeler have attempted to produce pyelonephritis experimentally in rabbits by the intravenous injection of colon bacilli obtained from human cases, but only eight of sixty-six animals injected had lesions in the kidney; twenty-one had lesions in other organs.[2] However, during the course of the work, while the urine of the animals was being controlled prior to injection, a rabbit with pyelonephritis was discovered. Cultures from this source injected into thirty-two rabbits produced lesions of the kidney in twenty-five, and in three only were other organs involved.[3]

These findings, together with the work of Brown,[4] Cunningham [5] and others, who obtained the tuberculosis bacillus from the urine of patients with pulmonary tuberculosis but with no complications, and the well known fact that the urine of typhoid patients contains the typhoid bacillus, show clearly that bacteria may penetrate the normal kidney.

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If lesions develop, special conditions, such as the peculiar infecting or localizing power of the bacteria, may be the determining factor. Thus Rosenow [6] has shown that following the intravenous injection of 220 different strains of streptococci, all from sources other than urinary infections, into 883 animals, only 9 per cent. showed lesions in the kidneys, whereas the localization into similar tissue or organs from which the strains were isolated occurred in a far higher percentage of animals. The tendency to localize selectively was so marked in some instances that only the specific organism could be recovered from the lesions even when mixtures of bacteria were injected, a selective action that Forssner [7] has shown can be produced artificially, for he found that bacteria when grown in kidneys or kidney extracts tend to localize in kidney tissue on animal inoculation. This phenomenon possibly explains the selective affinity of the strain of bacteria recovered from the rabbit with pyelitis, illustrating that the specificity might have been acquired and that the colon bacillus may not have been the original infecting agent.

Magoun [8] has shown that bacteria, like certain chemical substances, such as sodium bromid, are capable of being absorbed through the renal pelvis and recovered from the blood stream. Therefore, obtaining positive cultures of the colon bacillus in febrile reactions in urinary infections, although it proves that this bacillus is the cause of the patient's chill, does not prove that the source of the organism was not in the urinary tract. In fact, these febrile reactions occur so commonly following various manipulations in the urinary tract, such as the removal of residual urine, that the occurrence of the colon bacillus in the blood can well be attributed to absorption from the renal pelvis.

Rosenow's work on the elective localization of streptococci has suggested the possibility that oral sepsis, which often occurs in cases of pyelonephritis, may be the focus of infection for bacteria having selective affinity for the urinary tract. Moreover, cases of pyelonephritis have not been considered well treated unless possible oral foci were removed, but that they might be the source of a disease in which the colon bacillus seemed to be the predominating organism is hard to explain because of the low incidence of colon bacilli in oral foci of infection. However, the removal of foci and local treatment of the urinary tract, such as lavage, seemed to be rational therapy. But the

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many patients with pyelonephritis who return to clinics year after year for treatment by kidney lavage suggest that the treatment has been directed against the outcome, not against the cause of the disease. We have, therefore, studied a series of patients with pyelonephritis and dental sepsis and we have attempted to ascertain by intravenous injection of the bacteria into animals whether a relationship may not exist between the conditions.

The technic employed in isolating the bacteria and in injecting the animals was that used by Rosenow in similar studies. The material from the infected teeth or tonsils and the urine was spread on the surface of blood-agar plates and inoculated into tall tubes of glucose-brain broth. The cultures were incubated at from 35 to 37 C. The injections, from 3 to 5 c.c., were made intravenously with the primary culture in glucose-brain broth as soon as profuse growth had occurred, usually in from twelve to twenty-four hours. The viability and identity of the organisms injected were determined by plating on blood-agar. The growth thus obtained was then compared with that obtained on the blood-agar inoculated directly. The animals were anesthetized usually from three to six days after inoculation and thoroughly examined for lesions. Cultures were made routinely on blood-agar plates and in glucose-brain broth from the lesions and from the blood, bile, urine, joint fluids, kidneys, and spleen. The character of the lesions was determined by studying sections stained with hematoxylin and eosin, and the causative organism identified in the lesions by gram stain.

As noted in the case histories, the urinary infection was subacute in all of the cases studied.

REPORT OF CASES

Case 1 (328302).—Mrs. E. D., aged 30, came to the Clinic, Aug. 6, 1920. The patient's physician wrote that she had suffered for six or seven years with bladder trouble, manifested by frequent and painful micturition, the capacity of the bladder seeming to be limited to about 2 ounces. He suggested that this was the result of extravesical pressure. Eighteen months before he had removed the right ovary and tube, and the appendix, in the hope of relieving the condition of the bladder. The relief was only temporary, and the physician had suggested a hysterectomy. The patient was urinating every five minutes, and intervals greater than one hour were unknown. She dated her trouble from a pregnancy seven years before.

Physical Examination.—The physical examination was negative save for a rather marked suprapubic tenderness. The nose and throat failed to show anything suggestive of focal infection. Approximately fifty pus cells to the microscopic field were found in the urine, but many stained specimens failed to show tuberculosis bacilli. A test of kidney function showed a normal return of phenolsulphonephthalein; roentgenograms of the urinary tract were negative. Cystoscopic examination revealed a subacute areal cystitis. Urine obtained from the kidneys showed from one to five pus cells to the microscopic field, and contained colon bacilli. Roentgenograms showed five devitalized teeth and one infected root. Three of the devitalized teeth had definite areas of rarefaction in the apical region; two showed none.

Comment.—The cystoscopic findings and the history of the case seemed to indicate a previous rather severe pyelonephritis. The infection had localized in the bladder and apparently was kept up from some source of infection outside the urinary tract. The periapical infection of the teeth was believed to be this possible source. The devitalized teeth, including the two that did not show shadows, were surgically removed and from each pure cultures of green-producing streptococci were isolated.

Animal Inoculations.—Six rabbits were injected with the primary cultures in glucose-brain broth and all developed marked lesions in the kidneys (Fig. 1); one also had lesions of the bladder. The streptococcus was recovered from the lesions in the kidney in each rabbit.

Five animals were injected in the second animal passage. Lesions developed in the kidneys of four rabbits, and marked lesions in the bladder in one. One of the rabbits did not show lesions. Again the organism was recovered from lesions in the kidneys and reinjected into three rabbits. Lesions were found in the kidneys of all, but were less marked than those found in the kidneys of the animals in the first and second passages. Of the fourteen

Fig. 1.—Rabbit's kidney with marked swelling and edema of medulla, and areas of hemorrhage and necrosis four days after intravenous injection of streptococci obtained from an infected tooth of the patient in Case 1.

rabbits injected, lesions in the medulla appeared in thirteen, in the cortex in four, and in the bladder in two. Only one of the fourteen was negative. At necropsy the urine of eight contained albumin, pus cells and red blood cells, and seven either pus casts or granular casts. Four had lesions in organs other than the kidney and bladder, but these were relatively slight. Two of the animals had a few pin point hemorrhages in the stomach, another had a few lesions in the muscles, and a third had a small lesion in the myocardium.

Bacteriologic Investigation.—Cultures were made at necropsy from the kidneys, urine, spleen, bile, liver, blood, and joint fluids, whether or not lesions were present. In all the animals in this series the streptococci were recovered from the kidneys and urine. In ten of the animals all other cultures were negative. Four of the fourteen animals were found dead, and in these four the streptococcus was recovered from the blood, spleen, bile and liver, kidney and urine. In none of the animals did we find colon bacilli in either the kidneys or the urine. A culture made from a catheterized specimen of the

patient's urine early in the investigation showed only gram-negative bacilli. This culture was injected into two rabbits, one intravenously and the other into the bladder. Neither developed lesions of the urinary tract. September 28 the patient had the badly infected root removed. During the severe reaction which followed, the green-producing streptococcus appeared in the urine in large numbers, which still contained gram-negative bacilli. The mixed culture from the urine was injected into two rabbits. Both animals had lesions in the kidneys, and one had a hemorrhagic lesion in the bladder. Cultures from the lesions showed the streptococcus in both animals, and in one a few gram-negative bacilli. Cultures from the urine of both yielded the streptococcus, and of one a few gram-negative bacilli.

Case 2 (322852).—Mrs. L. S., aged 30, came to the Clinic July 3, 1920, with a history of having had an attack of grippe several months before, and occasional attacks of tonsillitis. She complained of frequent urination and dysuria, a constant pain over the bladder area, which became acute and sharp following urination, and marked loss of weight. At times she was obliged to void three or four times an hour, and stated that an hour and a half was the longest

Fig. 2.—Rabbit's kidney with multiple hemorrhages and small grayish necrotic-like areas in the medulla two days after intravenous injection of streptococci isolated from the lesions in the kidney of an animal previously injected with a suspension of pus expressed from the patient's tonsils in Case 2.

period of retention. The trouble dated from an attack of tonsillitis six years before.

Physical Examination.—The physical examination was negative save for some tenderness to deep palpation in the suprapubic region, and evidence of peri-urethral tenderness. A roentgenogram of the urinary tract was negative, and the test of kidney function showed a normal return of phenolsulphonephthalein. Twenty-six pus cells were found in the urine in a single microscopic field. Cystoscopic examination revealed chronic areal cystitis. From one to ten pus cells were found to the microscopic field in urine obtained with ureteral catheters. Colon bacilli were obtained on culture. A test of kidney function by the intravenous injection of phenolsulphonephthalein, with the ureteral catheters in place, showed a return of the dye from each kidney in two minutes; normal amounts were collected at the end of fifteen minutes. A pyelogram of the right kidney showed no evidence of pathologic change due

to infection. The tonsils appeared to have been badly infected previously. One impacted molar was shown in a roentgenogram.

Comment.—In this case the urinary infection had evidently persisted in a subacute form, producing but little, if any, damage to the kidneys, as their functional output remained normal and slight infection was demonstrable. The lesions producing the clinical symptoms evidently were the persisting areas of cystitis in the bladder. Because of the pathologic condition found in the tonsils, this also seemed a favorable case to investigate. At tonsillectomy adhesions were found between the capsule and the aponeurosis.

Animal Inoculation.—The predominating organisms found in the cultures made from the tonsils were green-producing streptococci and staphylococci. On first animal passage three rabbits were injected, one with a suspension of pus from the tonsils in saline solution, and two with the primary culture in glucose-brain broth. Lesions in the medulla and cortex were found in the

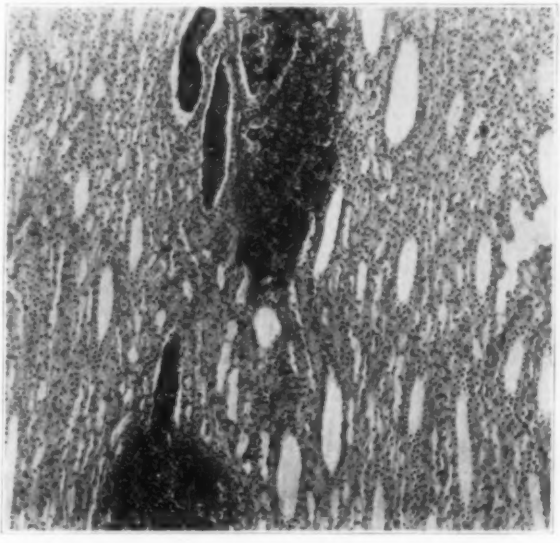

Fig. 3.—Section from rabbit's kidney, showing necrotic area with marked leukocytic infiltration, four days after intravenous injection of culture of streptococci obtained from an infected tooth of patient in Case 1.

three rabbits injected. Only the streptococci were recovered from the infected kidneys; these were reinjected into four other rabbits; two developed lesions in the kidneys (Fig. 2); two did not show lesions. In the third animal passage three rabbits were injected, two intravenously, and one intravesically, with the streptococci isolated from the infected kidneys of the rabbits injected in the second animal passage. There was no evidence of lesions in these rabbits.

Only two of the five rabbits in this series showing definite lesions in the kidneys had sufficient urine in the bladder at necropsy for urinalysis. The urine of both showed a slight trace of albumin and a few red blood cells.

CASE 3 (222711).—Mr. L. M., aged 21, came to the clinic Feb. 21, 1918, with a perirectal abscess that had been discharging for the past two years. Ten months before he had noticed blood in the urine and had experienced

pain at the end of micturition. He had noticed that if he took cold the urinary symptoms were exaggerated. At the time of examination he was obliged to urinate from three to five times at night and from eight to ten times a day.

Cystoscopic Examination. — This revealed an easily bleeding, excessively irritable bladder, with a capacity of but 3 ounces, and general diffuse cystitis of a tuberculous type. In passing urethral catheters up to the left ureter multiple obstructions were encountered. In the right side the catheter was passed without difficulty. Specimens from the right side were negative; those obtained from the left showed large amounts of pus. A diagnosis of left pyelonephritis, possibly tuberculous, was made and a nephrectomy performed. The removed kidney showed chronic pyelonephritis. The ureter was as large as a finger, thick walled, and definitely inflamed; the surrounding tissues were markedly edematous. Following this operation the patient's bladder symptoms improved, although they never completely subsided.

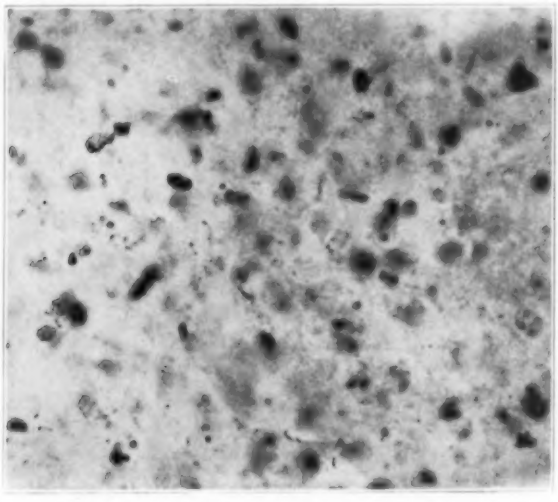

Fig. 4.—Diplococci and streptococci in and about leukocytes in the necrotic area shown in Figure 3.

Subsequent Course.—When the patient returned to the Clinic, Nov. 25, 1919, his urine still contained a large amount of pus, but repeatedly stained specimens were negative for tubercle bacilli, as were several guinea-pigs into which specimens of the urine were injected. Cystoscopic examination showed a persisting diffuse cystitis; a large amount of pus was obtained from the right kidney, but repeated stainings failed to show any tubercle bacilli. Kidney lavage with mercurochrome and silver nitrate was followed by improvement in the general condition of the patient. Four months later he was discharged, without dysuria, and able to retain his urine for one and one-half hours during the day. He was obliged to get up only twice during the night.

The patient returned to the Clinic a third time, Sept. 22, 1920, with his condition approximately the same. Cystoscopic examination at this time, however, showed but few pus cells in the urine of the right kidney. The teeth

were roentgenographed and the removal of two advised; both were definitely abscessed. The teeth were removed and an acute exacerbation of the urinary symptoms followed. The urine from the right kidney contained much pus and on culture gram-negative bacilli and green-producing streptococci were isolated. Cultures from the infected teeth showed a pure growth of the green-producing streptococcus.

Animal Inoculation.—Four rabbits were injected with the primary cultures. All the rabbits showed lesions in the kidneys, and three showed lesions in both kidneys and bladder. In one, in addition to the urinary lesions, a small hemorrhagic area was found in the stomach and in another a slight joint involvement. Three of the four animals had urine in the bladder at necropsy, and in all three red blood cells, pus cells, and a trace of albumin were found. A pure culture of the green-producing streptococcus was obtained from the kidney lesions of all the animals.

Case 4 (333893).—Mrs. L. H. P., aged 23, was examined at the Clinic, Sept. 14, 1920. She complained of constant pain in the bladder, worse when the bladder was full, and of being compelled to void twelve to fifteen times at night and every twenty to thirty minutes during the day. She had been cystoscoped several times prior to coming to the Clinic. She had an ulcerative cystitis, for which a vaginal cystostomy had been done two years before. This bladder condition had existed for eight years. The patient stated that a short time prior to its onset she had had four teeth devitalized.

Physical Examination.—The physical examination was negative. Examination of the nose and throat showed no evidence of a focus of infection. The renal function and blood urea were within normal limits. Urinalysis showed large numbers of pus cells and some red blood cells. A roentgenogram of the urinary tract was negative. Cystoscopic examination revealed a diffuse ulcerative cystitis of very severe grade. Specimens of urine obtained with ureteral catheter showed colon bacilli and a few short chain streptococci. The urine from the bladder contained a similar flora. A roentgenogram of the teeth showed the four devitalized teeth to be definitely abscessed. These teeth were removed surgically and cultures made from two; both yielded large numbers of the green-producing streptococcus. Marked exacerbation of symptoms followed removal of the teeth.

Animal Inoculation.—Four rabbits were injected. Lesions were found in the kidneys of three, and slight involvement in the joints of two. At necropsy the three rabbits with lesions in the kidneys had urine in the bladder with pus cells and red blood cells. The streptococcus was isolated from the kidneys of these animals, including the one which did not show gross lesions.

Case 5 (330369).—Mrs. E. B., aged 47, came to the Clinic, Aug. 19, 1920, for examination because of frequent and painful urination. The patient dated the onset of her trouble from an attack of rheumatism five months before. The attack had been preceded by a severe cold followed by urinary symptoms, which had grown progressively worse. At the time of her examination she was obliged to void hourly day and night.

Physical Examination.—The physical examination was negative, including the nose, throat and tonsils. One hundred cubic centimeters of blood contained 20 mg. of blood urea. Roentgenograms of the urinary tract did not show shadows suspicious of stones. A specimen of catheterized urine contained between 50 and 100 pus cells in the microscopic field. Cystoscopic examination revealed a very much irritated bladder with subacute diffuse cystitis. Specimens of urine obtained with ureteral catheters were filled with pus and on culture showed colon bacilli. A normal pelvic outline was shown in a pyelogram of the left kidney, and there was no evidence of structural changes as a result of the infection. An intravenous functional test with the ureteral

catheters in place showed a return of the dye from each kidney in three minutes; normal amounts were recovered fifteen minutes after injection. Roentgenograms showed six devitalized teeth and one root. The root and three of the teeth contained evidence of periapical infection. The remaining three did not show rarefaction.

Comment.—This case seemed favorable for study because of the apparent subacuteness of the infection and because the symptoms of the disease had been present only five months. The unimpaired kidney function and the normal kidney outline seemed to argue well for the general improvement of the patient if the source of the infection was removed and the resulting pyelonephritis checked. The infected teeth were removed surgically and an exacerbation of symptoms followed. A pure culture of green-producing streptococci was obtained from each.

Animal Inoculation.—Four rabbits were injected with these cultures; one died within the first twenty-four hours, and did not show lesions. Two of the rabbits had lesions in the kidneys, one also had lesions in the bladder. Cultures from the third rabbit were negative. Streptococci were recovered from the lesions in the kidneys and injected into two other rabbits. One had lesions in the kidney, the other, lesions in the bladder. The lesions in the kidneys were in the medulla, similar to those shown in Figures 1 and 2, and those in the bladder were in the mucosa and submucosa. No gross lesions were found outside the urinary tract.

A pure culture of the green-producing streptococcus was obtained from the kidneys and urine of the two animals with lesions of the kidneys. Cultures made from bile, spleen, joint fluid, and blood were negative. In the animal with bladder lesions only, cultures from the kidney were negative, although the urine contained streptococci. Examination of the urine at necropsy showed albumin, pus cells, red blood cells, and granular casts in three rabbits. In the fourth rabbit there was only sufficient urine to culture.

Case 6 (332441).—Mr. N. R., aged 25, came to the Clinic Sept. 2, 1920, complaining of general malaise, inanition, and insomnia. He had no symptoms of urinary trouble and his general examination was negative.

Examination.—Roentgenograms of the teeth showed periapical infection at the roots of four. The tonsils were large and filled with fluid pus. A large amount of pus and an occasional blood cell were found in the urine. Stained specimens were negative for the tuberculosis bacillus. The kidney function was normal as tested by phenolsulphonephthalein. Cystoscopic examination revealed chronic diffuse cystitis with purulent urine. Specimens obtained with ureteral catheters revealed many pus cells in the microscopic field, and on culture colon bacilli were found. The intravenous phenolsulphonephthalein test gave a normal return of the dye in fifteen minutes. It was difficult to determine the duration of the disease because of the lack of urinary history, but as the patient had been in poor general condition for seven months the case seemed favorable for study. The tonsils were removed and cultured and produced countless numbers of green-producing streptococci and many staphylococci.

Animal Inoculation.—Two rabbits were injected with emulsion of the extirpated tonsils and two with the cultures in glucose-brain broth. The four animals had lesions of the kidney, two had lesions in the kidney and bladder, three slight lesions in the muscles, and one a small lesion in the myocardium. A pure culture of the green-producing streptococcus was obtained from the lesion in the kidney of each rabbit.

SUMMARY

In the foregoing six case histories there is undoubted clinical and cystoscopic evidence of pyelonephritis, accompanied by various degrees

of cystitis. In none of these cases was there any urinary obstruction, either from stone, stricture or prostate, to which the urinary infection might be attributed.

The duration of the disease varied greatly; the longest duration of symptoms, which was eight years, followed the devitalization of four teeth; the shortest duration was five months in a case in which urinary symptoms first occurred following an attack of rheumatism. In one case repeated attacks of grippe and tonsillitis were considered possible etiologic factors, and in three cases the clinical histories gave no suggestion of the source of the infection.

The teeth of the patients had little or no caries; three had a slight degree of pyorrhea. In five of the six cases twenty-one infected teeth, two infected roots, and one impacted tooth were found. Nineteen of the twenty-one infected teeth had been devitalized; in the other two pulp infection followed extensive filling. Sixteen showed periapical infection; five did not show apical rarefaction. Cultures from all but the impacted tooth, which was sterile, produced green-producing streptococci. The primary cultures in glucose-brain broth were injected intravenously into twenty-seven rabbits. Twenty-four (89 per cent.) had lesions in the kidney, and eight lesions in the bladder, four lesions in the muscles, three lesions in the stomach, three lesions in the endocardium, two lesions in the myocardium, and four had joint involvements. The lesions outside the urinary tract were relatively slight in each instance.

RESULTS OF ANIMAL INOCULATION

	Strains of Streptococci	Animals Injected	Animals With Lesions in							
			Kidneys	Bladder	Kidneys and Bladder	Joints	Muscles	Stomach	Endocardium	Myocardium
On isolation.....	6	27	24	8	8	4	4	3	3	2
On second animal passage...	3	11	7	2	1	0	1	1	0	1
On third animal passage.....	2	6	3	0	0	0	0	0	0	0

In the second animal passage, the rabbits were injected with streptococci isolated from the kidneys of rabbits that had lesions following injection of the streptococci in the first animal passage. Eleven rabbits were injected with cultures from three strains. Seven rabbits (63 per cent.) had lesions in the kidneys, one rabbit had lesions in the kidneys and bladder, and one had lesions in the bladder. One had slight lesions in the muscles, one in the stomach, and one in the myocardium.

In the third animal passage, six rabbits were injected with cultures

from two strains. Three developed lesions in the kidneys. None of the six showed evidence of lesions in any of the other organs.

The lesions in the kidneys of the rabbits in the first and second animal passages were pronounced (Fig. 3); in the third passage, as affinity for the urinary tract became slighter, the lesions became less marked.

That the marked affinity of these strains for the urinary tract has significance and was not accidental seems certain because during the injection of 208 animals under the same conditions with streptococci from patients having diseases other than urinary infection, only seven developed lesions in the urinary tract. Moreover, experiments in which pus expressed from patients' tonsils was injected without incubation seem to demonstrate that the selective localization of these streptococci was not due to their incubation in artificial mediums or to an overwhelming dosage resulting from their increase in numbers, but to the selective action of the organism isolated. The selective affinity of the streptococci for the urinary tract was so marked that although a mixed culture was injected into some of the animals the streptococcus alone was recovered from the lesions.

Specimens of catheterized urine from all the rabbits were normal before injection; after injection a small amount of albumin with relatively few red blood cells, epithelial cells, and a larger number of leukocytes were usually present.

The kidneys of the animals were usually about normal in size or slightly swollen, and in no instance was the picture that of diffuse parenchymatous nephritis, but always that of localized infection. The capsule stripped readily in all. The cortex often presented small, opaque, yellowish-white areas, and on section the cut surface often revealed marked swelling and edema, especially of the medulla, sometimes associated with areas of hemorrhage varying in size from 1 mm. to 4 mm. Varying numbers of necrotic areas were found in the medulla, some areas so small they were scarcely visible, others large, grayish-white streaks, necrotic-like in appearance, and gradually disappearing as they approached the cortex. These areas were surrounded by zones of congestion and hemorrhage. In only a few instances were hemorrhagic lesions found in the ureters.

On microscopic examination, no evidence of diffuse nephritis was found. The glomeruli were almost wholly free from lesions other than varying degrees of congestion. The necrotic areas showed marked destruction of the epithelium and marked leukocytic infiltration. The parenchymatous cells immediately surrounding these areas were often granular and swollen, and the nuclei of many failed to take the stain. Sections stained by the Gram method showed varying numbers of gram-positive diplococci, singly, in groups, or in short

chains (Fig. 4). The leukocytes often contained many diplococci in various stages of digestion, depending on the duration of the experiments.

CONCLUSION

It seems from our study that pyelonephritis may often be due to focal infections harboring streptococci which have a selective affinity for the urinary tract, and that the colon bacillus which is commonly found and generally believed to be the cause, is of secondary importance.

MUSCULAR INFANTILISM

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Diseases of the nervous system form a somewhat obscure branch of medical science. Our ignorance of the morbid anatomy and histology of many of them is profound. It is, accordingly, a matter of no surprise that our classification of these diseases is unsatisfactory. The intimate correlation between nervous and muscular systems is recognized in the fact that under nervous diseases, every textbook includes descriptions of conditions which are, so far as known, essentially muscular.

There is a tendency to segregate those cases which show muscular atrophy into two clinical groups, the atrophies and the dystrophies. The distinction is probably not well grounded, in respect to etiology. In view, however, of our lack of knowledge of the cause of most of the nueuromusclar diseases, even this criticism must be made somewhat tentative. We can recognize the grosser causes of lack of function of the central nervous system, such as cerebral hemorrhage, or an attack of meningitis, but we know very little of the factors which maintain the central nervous system as a going concern; even in the case of the much simpler muscular system there are many unsolved conundrums. Why is creatin always present in muscle? Does it originate in muscle or is it carried from the outside? What mechanism in the muscle transforms it into creatinin, and what is the value of this apparently essential substance in the muscular economy? With the nervous element in the neuromuscular complex remaining shrouded in mystery, there is little cause for wonder that such comparatively common conditions as disseminated sclerosis, progressive muscular atrophy, or pseudohypertrophic paralysis, remain unexplained.

The essence of scientific experiment is to vary one factor at a time, the others remaining constant. In the case of the human subject, it is difficult, almost impossible, to predicate these conditions, but an approximation to them in which there is one outstanding clinical variation from normal and along with it one outstanding chemical variation from normal has come under notice. In the belief that it is a valuable case I venture to place it on record.

REPORT OF CASE

R. W. T., aged 26, single, bank clerk, consulted me Sept. 25, 1917, because of his inability to perform any unusual exertion, or, in fact, anything more than a comparatively small muscular effort would accomplish. There was no history of tiring easily; provided, the muscular work called for was small in

intensity, the effort could be maintained as long as it could be by the ordinary person, but when the effort called for was more than a very small amount, it simply could not be performed. Thus he could walk about all day, and perform to the full his duties as a bank clerk; he could enjoy a game of golf, but

TABLE 1.—PATIENT'S FAMILY HISTORY ON FATHER'S SIDE

"Dad's" Grandmother, affected	1. Female, affected, "Dad's" mother	1. Female, affected, still living, 75, six in family	1. Male affected (1. Male, free; 2. Male, free)
			2. Male, affected, no family
			3. Female, free, no family
			4. Male, free, two children, both free
			5. Male, affected, unmarried
			6. Female, affected, no family
		2. Female, affected, still living, 73	1. Male, free, do not know about family
			2. Male, affected, unmarried
			3. Female, free, two children
		3. Female, free, died at 36 years, inflammation of bowels	1. Male, free, no family
			2. Male, free, no family
			3. Male, affected, unmarried
		4. Male, free, still living; seven children, all free	
		5. Female, free, died at 18, summer complaint	
		6. Male, affected, still living	1. Male, free, 1 male, free I think
			2. Female, free, no family
		7. Male, affected, (father of R.W.T.), still living	1. Female, free (1. Male, free; 2. Female, free)
			2. Female, affected, unmarried
			3. Male, affected, unmarried
			4. Male, free, unmarried
			5. Male, affected, (R.W.T.)
			6. Female, free
		8. Male, affected, died at 45, Bright's disease	1. Male, five children, all free
			2. Female, free
			3. Male, affected
			4. Female, free, three children, don't know about them
			5. Male, affected
			6. Female, free, no family
			7. Female, free, unmarried
			8. Female, free, unmarried
		9. Female, affected, died at 53, cancer	1. Female, free, unmarried
			2. Male, free
			3. Female, affected, unmarried
		10. Female, died at 3	
		11. Female, free, died at 27, consumption	1. Male, free, unmarried
			2. Female, free, died
	2. Female, affected, "Dad's" aunt	1. Female, free, died, don't know about family	
		2. Male, affected, no family	
		3. Male, free, family free	
		4. Male, free, don't know about family	
		5. Female, affected	1. Male, free
		5. Female, affected	1. Male, free
			2. Male, free
		6. Female, free, family all free I think	
	3. Female, free	7. Male, affected	1. Male, affected
			2. Female, free
		8. Male, family free so far as I know	

throwing a baseball or rowing a boat were sheer impossibilities, while even such ordinary activities as taking a high step or rising from a sitting to the upright position without the assistance of his hands, were difficult. He had been aware of this condition since he was a child. His health has always been good, and within limits his enjoyment of physical activity has always been

as great as that of his neighbors. The physical limitation has never been associated with mental weakness or psychic change of any sort, apart from the recognition that his muscular weakness handicapped him in juvenile sports. He knows that his father, and his father's mother have the same weakness.

Family History.—It was possible to obtain a fairly complete family history, dating back to the patient's paternal great grandmother, and passing down through his paternal grandmother and his father to himself. From a study of Table 1 it will be seen that the condition affects both male and female, that with one exception—if the observation be correct—those who are themselves free from the condition, whether male or female, do not transmit it to their children. That exception is the third oldest of "Dad's" sisters, who while free herself had a son who is affected. This individual, my patient states, is much the worst of all, being "pretty helpless." It further shows that the condition is not one which predisposes to any particular disease, does not of itself shorten life, and in no way interferes with the reproductive powers. Analysis of Table 1 shows further that of twenty-six males liable to be affected, fourteen were so affected, and twelve were free. Of twenty-one females, seven were affected while fourteen were free.

TABLE 2.—PHYSICAL MEASUREMENTS OF PATIENT

	Left, Inches	Right, Inches	Inches
Biceps	9⅝	10	
Forearm	8¾	9¾	
Wrist	5½	5⅝	
Thigh	21¼	22	
Leg	13	13	
Knee	13¼	13¼	
Calf	14	14	
Ankle	8¼	8¼	
Chest			38
Waist			32½
Abdomen and hips, at most prominent circumference			38⅝

Physical Examination.—Examination shows apparently little departure from the normal. The patient is 5 feet 8 inches tall and weighs 155 pounds. He is distinctly adipose, the fat being largely distributed in the general subcutaneous tissue, so that there are rounded outlines suggestive of the female rather than the male figure. This suggestion is accentuated by the presence of striae over the lower abdomen and upper part of the thighs, some of these being white and glistening, others purplish, exactly like typical "striae gravidarum." He has no recollection when these appeared. He underwent no sudden or even rapid increase in bulk, and is not now thinner than he has been, so that the explanation of the striae is somewhat obscure. This relative adiposity is, the patient states, not characteristic of the condition. He is himself, he says, the only one he knows of who shows it. The majority of those affected are normal in outline, all, however, being characterized by the presence of small bones. The probability is that the smallness of the bones is directly correlated with the limited power of the muscles. The wrist measurement, for example, in this case is about 5½ inches. The average female wrist is about 6 inches, and the average male wrist is about 6¾ inches.

Two other characteristics of those affected are the presence of distinctly square shoulders and a short neck.[1]

1. A fairly complete examination has been made from time to time, and in this respect I am indebted to Professor Swale Vincent, of the Department of Physiology, University of Manitoba, now of the University of London, to Professor William Boyd of the Department of Pathology, University of Manitoba, and to Dr. Robert G. Armour of Toronto, for observation along special lines.

Examination of the circulatory, respiratory and alimentary systems revealed no abnormality. The blood pressure (systolic) has varied from 130 to 140. The urine has shown no albumin, blood, sugar or pus. The thyroid is very slightly enlarged.

Blood Examination.—Investigation of the blood was done from time to time. The red cell count has always been above normal, varying from 6,230,000 to 5,760,000. The leukocyte count has always been about normal, the highest observation being 12,400, the lowest 7,600. The hemoglobin is also within the limits of normal variation, from 75 to 90 per cent. being the limits. This, it will be observed, gives a rather lower color index than normal.

The differential leukocyte count has followed at all times strictly normal lines, averaging: polymorphonuclears, 75 per cent.; small lymphocytes, 20 per cent.; large lymphocytes, 3 per cent.; eosinophils, 2 per cent.

Roentgen-Ray Examination.—Roentgenograms were taken of the skull with a view to determining whether or not there was any increase in the size of the pituitary fossa. No variation from normal has been observed.

Examination of the Central Nervous System.—This examination was made at my request by Dr. Robert G. Armour of Toronto. His report is as follows:

Feb. 5, 1919: Shoulders broad and high; pelvis narrow; musculature of thighs apparently good, tapering markedly from hips to knees; calves well developed; musculature of arms poor, about size of those of boy of 16; no obvious wasting of any particular muscle or group; fingers moderately small and tapering, not deformed; toes slightly "hammer"; in standing, appear to spread. He has always had trouble in getting boots to fit him on account of the width of the feet at the base of the toes. Marked callosities under transverse arch of feet. Station, with eyes closed, good. On either leg alone and eyes closed, fair. On left not quite so steady as on right. Tends to trip or slip easily. Gets up from a lying position fairly readily, with no attempt to "climb up" himself. Can walk on toes, but has difficulty in rising on heels. No appearance of atrophy of peroneal muscles. Moderately good strength of leg muscles, although below average, and low in proportion to appearance of development. Strength of biceps and triceps of arms inconsiderable.

Grasp of hands each 16 on dynamometer (average normally 45). No inequality in strength of facial muscles of two sides. Retraction of mouth not well performed, and extreme efforts cause little wrinkling of the face. No apparent weakness of upper face. Mouth opened and tongue protruded, and palate elevated to full extent and in middle line. No ptosis. Eye movements full in all directions. No nystagmus. Pupils react briskly to light and accommodation. Fundi normal. Moderate pes cavus.

Reflexes: Knee jerk present, easily elicited, not increased, no clonus. Idiomuscular contractility not obtained over quadriceps extensor. Ankle jerk easily elicited, no clonus, equal, idiomuscular contractility obtained in calf muscles. Attempts to elicit this in extensors and peroneals cause contraction of the calf muscles which raise the heel from the ground. When this is prevented, no idiomuscular contractility is obtained. Biceps and triceps reflexes of upper extremity easily elicited. Idiomuscular contractility present in triceps, extensors of forearms and doubtful in deltoids. Not present in biceps, pectorals or trapezii. Present to a slight degree in the facial muscles. Plantar, plantar flexion, but feeble. Cremasteric reflex doubtful. Abdominal and epigastric reflex doubtful.

No sensory change demonstrable, including position sense. No tachycardia. All muscles react to faradism.

Examination of the Eyes.—This examination was made for me by Dr. Harvey Smith. His report is: "I find that he has a small error of refraction. Fundus examination is negative, nor can I discover any defect in his field or in his pupillary reflexes."

The Wassermann reaction was negative. There was slight enlargement of the thyroid gland.

Treatment.—At the suggestion of Professor Swale Vincent, raw suprarenal glands were administered. One ox gland per day was taken, minced, as a sand-

wich, commencing Nov. 1, 1917. This was continued until Dec. 18, 1917, when because of some nausea this feeding was stopped. Ergographic tracings made before and after the administration of suprarenal gland seemed to indicate slight improvement in the muscular condition, but it was not striking.

Jan. 25, 1918, suprarenal gland feeding was resumed at the rate of one-half ox gland per day. This was continued until March 14, 1918. No appreciable increase of muscular power was noted, although there was some gastric instability. The taking of suprarenal gland was, therefore, definitely stopped.

May 17, 1918, a course of graduated exercises was commenced. These were of a simple nature designed with a view to increasing the existing muscular development. They were continued until June 26, 1918, when there was added to the exercises a course with the Bristow coil, an instrument which in other cases has proved of considerable value in increasing the bulk of atrophied muscles.

Oct. 15, 1918, his measurements were again taken.

TABLE 3.—Physical Measurements Eleven Months After Treatment Was Begun

	Left, Inches	Right, Inches	Inches
Biceps	10	10⅛	
Forearm	9¼	9⅝	
Wrist	5½	5½	
Thigh	21⅞	22	
Leg	13⅜	13⅝	
Knee	13½	13½	
Calf	14	14½	
Ankle	7⅝	7⅝	
Chest			38
Waist			33
Abdomen and hips			39½

These measurements are confirmatory of the opinion expressed by him that his muscular power was little, if any, increased.

Subsequent Course.—In the spring of 1919, the patient had an attack of influenza and was ill for three weeks. The summer he spent at work in the country and I did not see him again until Sept. 22, 1919. The measurements then were as follows:

TABLE 4.—Physical Measurements Eleven Months After Cessation of Treatment

	Left, Inches	Right, Inches	Inches
Biceps	10	9⅞	
Forearm	8⅞	9⅜	
Wrist	5⅝	5⅝	
Thigh	21½	21⅜	
Leg	13	13¼	
Knee	13½	13½	
Calf	14	14½	
Ankle	7⅝	7⅝	
Chest			39
Waist			33
Abdomen and hips			38

These show practically no alteration from those previously noted. In other words, he seemed to be as well without treatment of any sort as with it.

The muscles themselves, though not at all massive, are not abnormally small for a man of his build. The electrical reactions were tested and gave a response of normal quality to both faradism and galvanism. A small piece of muscle was excised from the right vastus lateralis muscle and sent for histologic

examination to Professor William Boyd. His report indicates practically no departure from the normal.

Microscopic Examination.—Portions of the vastus lateralis muscle, removed under local anesthesia, were examined by the usual methods. The only marked deviation from the normal was the wide separation of the muscle fibers from one another by what appeared to be edematous fluid. This, however, was probably merely the result of the injection of novocain. The individual muscle fibers appeared to be slightly atrophic, but the transverse striations were quite distinct, although, perhaps, not quite so prominent as in the normal fibers. The nuclei of the sarcolemma were well developed. There was no evidence of any of the increase of fat which is so characteristic a feature of the pseudohypertrophic form of muscular dystrophy.

From April 20, 1920, until June 6, 1920, thyroid gland was given, 15 grains per day. During treatment with thyroid gland he had an excess of carbohydrate. The result of this was certainly not an improvement clinically, and examination of the urine suggests that the results were bad. Pituitary extract. 15 grains per day was taken from June 14, 1920, until July 7, 1920. Again no improvement was shown. Strychnin, $\frac{3}{65}$ grain, was also used from Sept. 13, 1920, until Sept. 20, 1920, with equally unfavorable consequences.

From time to time the patient has been examined by Prof. Swale Vincent and by Prof. A. T. Cameron. Professor Vincent's report is as follows:

March, 1920: The patient has a fairly good power of long sustained effort of a low grade. He walks fairly well and can play eighteen holes of golf without much fatigue. He can raise a 25 pound bar above his head four or five times. He can hang onto a horizontal bar for a moment, but cannot raise himself in the least. There has been some increase in the strength of his arms since 1917.

The dynamometer record has also slightly improved since 1917. The results have varied between 40 and 50 kilograms tested by Verdin's (Boulitte's) dynamometer. Mosso's ergograph has not given very accurate results because of the long time during which the patient could continue minimal contractions. With the right second finger the laboratory attendant could execute 400 kilogram centimeters of work when each complete movement was carried out in two seconds. The patient could only raise the weight five or six times, doing at most from 12 to 15 kilogram centimeters of work. Roughly, then, his muscular power is about 4 or 5 per cent. of the normal.

CHEMICAL REPORT

The observations have been carried out between March and October, 1920. As during this period the patient was carrying out his usual duties, it was impossible to conduct an exact supervision of diet. As soon as the creatinuria was definitely associated with his condition, futher observations were directed chiefly to the effect of treatment on this symptom. As the degree of creatinuria did not appear to be materially affected by a moderate meat diet, no special diet conditions were imposed, but full particulars were obtained of the nature of the meals on the days on which twenty-four hour urine samples were obtained.

Urine Examination.—The following methods were employed: The total phosphates were estimated by the uranium acetate method. Chlorids were estimated by the Volhard-Arnold method. Uric acid was determined by the Benedict-Hitchcock modification of the Folin-Macallum-Denis procedure. Acidity and total ammonia and amino-acids were estimated by the formol titration method. Creatin and creatinin were determined by the Folin-Benedict method, using a Kober colorimeter. The creatin figures are expressed in terms of creatinin. Urea was approximately determined by the Hinds-Doremus ureometer.

Nothing specially abnormal was observed in the color, appearance or specific gravity. Indican was only present in normal amounts. The acetone bodies (tested for by Le Nobel's, Gerhardt's, Hurtley's, and Rothera's reactions) were almost invariably absent. The exceptions are noted. Reducing sugar and albumin were invariably absent. Urinary sediments were not abnormal.

The figures in Table 5 refer to grams in the twenty-four hour sample, except those for acidity, expressed in cubic centimeters of tenth normal alkali.

May 9, an extremely hot day, more water than usual was drunk, less urine than usual was excreted, and the Le Nobel and Gerhardt tests for aceto-acetic acid, and the Rothera test for acetone were distinctly positive. June 11, the Rothera test was positive, the Le Nobel test just positive, and the Gerhardt test negative.

TABLE 5.—Results of Examination of Urine

Date	Total Volume in C.c	Acidity	Ammonia and Amino-Acids	Urea	Uric Acid	Phosphates	Chlorids	Creatinin	Creatinin plus Creatin	Creatin	Diet
3/ 2	1,050	252	0.43	22	0.43	2.56	.....	1.09	1.47	0.38	Normal; some roast beef
3/ 9	2,250	445	0.82	27	0.51	2.41	9.27	0.81	1.72	0.91	Meatless on March 8 and 9
3/31	1,725	642	1.12	17	....	....	16.56	0.90	1.31	0.41	Normal; meat with two meals
4/16	1,785	512	0.94	32	....	2.4	.....	1.45	1.80	0.35	Normal; some fish
4/17	1,345	439	0.92	30	....	2.1	.....	1.26	1.84	0.58	Meat with two meals
4/18	2,040	414	0.81	28	...	1.9	.....	1.22	1.71	0.49	Somewhat less meat
4/27	1,445	...	....	..	....	2.05	.....	0.90	1.52	0.62	Meatless, thyroid from April 20; with excess sugar
5/ 7	1,575	431	0.68	28	....	....	.....	0.85	1.70	0.85	Some fish; thyroid; sugar
5/ 8	1,250	393	0.75	21	....	....	.....	0.90	1.30	0.40	Meatless; thyroid; sugar
5/ 9	790	458	0.78	21	....	. ..	.....	0.85	1.42	0.57	Some meat; thyroid; sugar
6/ 4	1,300	1830	1.80	21	....	2.4	.....	1.14	1.24	0.10	Meatless; thyroid; sugar
6/ 5	1,350	945	2.12	22	....	2.4	.....	1.12	1.28	0.16	Meatless; thyroid; sugar
6/ 6	1,240	840	1.42	22	....	2.4	.....	0.95	1.24	0.29	Chicken; thyroid; sugar
6/11	1,440	490	1.04	30	0.78	....	.....	1.48	2.20	0.72	Fish and meat; thyroid stopped since June 6; excess of sugar continued
6/29	1,300	343	0.98	21	....	....	.....	1.09	1.52	0.43	Some meat; pituitary and excess sugar since June 23
6/30	1,470	448	0.81	21	....	....	.....	1.04	0.59	0.55	As previous day
7/ 1	1,750	296	0.62	18	....	....	.....	0.81	1.16	0.35	As previous day
8/27	1,050	...	....	..	....	....	.....	1.33	1.89	0.56	No treatment; some fish
8/28	1,330	...	....	..	....	....	.....	1.33	1.85	0.52	As previous day
8/29	1,145	...	....	..	....	....	.....	0.94	1.25	0.31	Meatless
9/19	1,005	245	0.60	..	....	....	.....	0.89	1.37	0.48	Some meat; strychnin since September 13
9/20	1,870	274	0.75	..	....	....	.....	0.82	1.27	0.45	As previous day
9/21	1,760	289	0.62	..	....	....	.....	0.86	1.21	0.35	As previous day, but strychnin stopped September 20

While the urea figures are distinctly low, the only distinct abnormality is the continual presence of creatin. The creatinin excretion for a man of about 68 kg. with some body fat should be about 1.4 gm. per day. The figure in Table 5 is almost always less, and is only three-fourths of this on a meatless diet. There is some indication that the excretion of creatin tends to diminish slightly on a meatless diet, though the results for meatless days include the highest figure recorded. The creatin figures are consistently high, varying between 40 and 110 per cent. of the creatinin figures.

Administration of thyroid with excess cane sugar caused for several weeks an increase in the amount of creatin, in agreement with the observation of Cramer and Krause that thyroid medication causes creatinuria, and the occurrence of creatinuria in exophthalmic goiter. Continued administration of thyroid over a prolonged period, while apparently increasing the creatinin toward

a normal figure, and giving the lowest degree of creatinuria recorded, produced marked acidity, with a concomitant feeling of the patient that he was not so fit, and a distinct decrease of muscular strength, as indicated by the ergograph, so that the initial rise of creatin can be regarded as indicating an adverse effect. The cause of the marked hyperacidity was not ascertained. It was not due to increase of phosphates, nor to acetone bodies nor to lactic acid.

Pituitary produced no effect. Strychnin appeared to decrease the creatinin without producing any effect on the creatin. This effect can, perhaps, be regarded as nonbeneficial, in line with the general effect on the patient and the ergographic record.

In order to study the creatinuria more closely, the urine was collected at three hour intervals on Sunday, September 5. A final collection was made for the nine hour period ending at 8 a. m. September 6. In this, as in previous work, the patient's accuracy had to be relied on. The total amount passed was very low, but assurance was given that the amount was collected accurately. The diet was meatless, otherwise normal, and the patient had been undergoing no special treatment for the previous two months. The results are shown in Table 6.

TABLE 6.—RESULTS OF STUDY OF URINE WITH PATIENT ON A MEATLESS DIET AND UNDER NO SPECIAL TREATMENT

Time	Volume, C.c.	Acidity, C.c.	Ammonia Plus Amino-Acids, Gm.	Creatinin, Gm.	Creatin, Gm.	Acidity per 100 C.c.	Ammonia Plus Amino-Acids, Gm. per 100 C.c.	Creatinin, Gm. per 100 C.c.	Creatin, Gm. per 100 C.c.
11 a. m.	180	41	0.031	0.15	0.09	23	0.073	0.08	0.05
2 p. m.	100	35	0.077	0.11	0.04	41	0.077	0.11	0.04
5 p. m.	85	31	0.069	0.12	0.05	37	0.081	0.14	0.05
8 p. m.	72	34	0.069	0.08	0.05	47	0.096	0.11	0.07
11 p. m.	44	31	0.053	0.06	0.03	71	0.121	0.14	0.07
8 a. m.	215	150	0.294	0.27	0.12	70	0.137	0.13	0.06
Total	696	322	0.69	0.79	0.37				

These results, especially when expressed per 100 c.c. of urine, indicate that the creatin concentration in the urine is approximately constant throughout the twenty-four hours, but tends to increase slightly with increased acidity and ammonia. The creatinin figures do not show this relationship. This constant excretion of urine throughout the twenty-four hours is not in accordance with other observations on cases of creatinuria. It will be discussed further elsewhere.

Blood Sugar.—Blood sugar was estimated April 2. A sample was taken in the morning, before breakfast. One-tenth per cent. glucose was present (Benedict's modification of the Lewis and Benedict method). A breakfast was given consisting of 200 c.c. of milk, 100 gm. bread and butter, and 100 gm. glucose. After two hours the blood sugar was 0.15 per cent. The urine contained no reducing sugar throughout the day, and the feces contained none on this nor on the two succeeding days.

Sugar Tolerance.—April 11, two hours after a moderate breakfast, a similar sugar meal was given, with cane sugar substituted for glucose. No reducing sugar was detectable in the urine throughout the day. The carbohydrate metabolism was, therefore, apparently normal.

Blood Creatinin and Creatin.—A sample of blood was obtained Nov. 28, 1920, two hours after breakfast. The creatinin estimated by Folin's method, amounted to 0.7 mg. per 100 c.c. blood. This is the minimal figure for normality. The creatin was not determined, since according to Hunter and Camp-

bell[2] and Feigl[3] the present methods do not yield results sufficiently accurate to warrant any conclusions being drawn. A sample of urine obtained at the same time showed, per 100 c.c., 113 mg. creatinin and 46 mg. creatin.

It may be noted that the blood appears to clot somewhat more readily than normal.

Comment.—Most of the interest of Professor Cameron's report centers around the presence of creatinuria. In considering the results of examination, one must bear in mind the fact that during the whole time of observation the patient has been engaged in his ordinary work. Modifications of diet were for the most part carried out without control. The patient has lent himself to investigation in the most willing and intelligent manner.

The chemical findings may be summarized as follows:

1. The creatinin excretion suggests the actual extent of musculature which he possesses.
2. The creatin excretion suggests an infantile condition.
3. The creatin + creatinin excretion is in agreement with the musculature of a normal individual of his build.
4. The creatin excretion varies little on meat diet.
5. The blood sugar is normal.
6. Sugar utilization is normal.
7. Acetone bodies were present on one occasion only. The creatin for this day was not a maximum. Acetone bodies have no special relation to this condition.

Regarding the influence of treatment it may be said that:

1. During suprarenal administration no chemical examination was made, Professor Cameron being still on active service.
2. During thyroid administration excessive carbohydrate was used without obviously modifying the thyroid effect. (a) There was initially a slight increase in creatin which lasted two or three weeks. (b) After six weeks there was a marked fall in creatin and no appreciable change in creatinin. (c) There was marked acidity of the urine, cause undetermined.
3. Pituitary had no effect. This was noted in spite of carbohydrate being still used in excess.
4. Strychnin apparently decreased creatinin without any marked effect on creatin. This was accompanied by unfavorable ergographic records. Subjectively, the physical condition was also less satisfactory. (Other factors may have entered here to contribute to this.)

Result of a twenty-four hour test on meatless diet was:

1. Creatin was excreted constantly.
2. There was no particular relation to creatinin.

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2. J. Biol. Chem. **33**:169, 1918.
3. Biochem. Ztschr. **105**:255, 1920.

3. There was increase of creatin with increase of ammonia and acidity.

4. Creatin excretion did not fall off during the night.

5. The kidneys removed creatin from the blood at a fairly constant rate per c.c. of urine.

A word or two is necessary regarding the ergographic tracings. The earlier ones are comparatively valueless on account of the fact

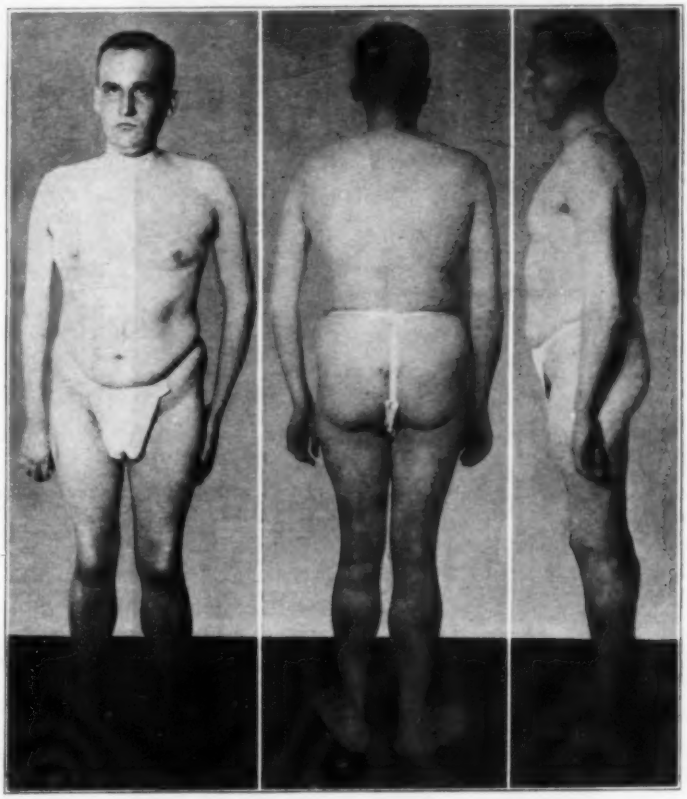

Fig. 1.—Three views of patient showing amount and deposition of fat.

that a small load was used; the patient was able to raise this almost indefinitely; in other words, for a small load his endurance was considerable. In this respect the tracing is infantile in character.

In the later tracings a load of 2,000 gm. was used and in most cases the observation was controlled by a corresponding observation on the laboratory attendant. In every case, the load was 2,000 gm. and each complete movement was carried out in two seconds.

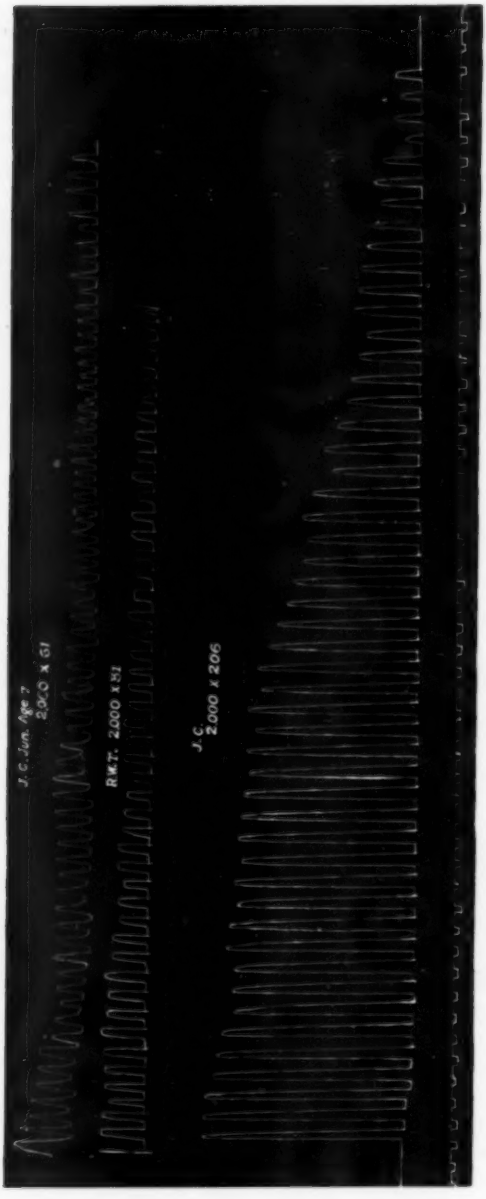

Fig. 2.—Ergographic tracing.

Table 7 shows a tracing of R.W.T., J.C., (the laboratory attendant), and J.C., Jr., the son of the latter, aged 7 years 2 months. With a load of 2,000, the child has an excursion of 61, as against R.W.T.'s average which is well under 40. This child was still normally excreting creatin.

The observation on May 9, 1920, corresponds to a time when he had been taking thyroid, 15 grains, per day for about twenty-one days. The tracing of June 6 was taken on the last day of thyroid administration and showed a drop to 10, the lowest recorded in the series. The dynamometer record on this day was 40, so that the loss was in endurance rather than in power. On all grounds, therefore, the taking of thyroid produced undesirable results.

TABLE 7.—Ergographic Tracings of Patient and Two Normal Subjects

Date	Name	Excursion	Dynamometer
5/ 9/20	R. W. T.	36	
	J. C	206	
6/ 6/20	R. W. T.	10	40
	J. C.	249	
6/12/20	R. W. T.	21	38
	J. C.	226	
7/ 2/20	R. W. T.	36	39
	J. C.	230	
9/12/20	R. W. T.	39	40
	J. C.	230	
9/21/20	R. W. T.	26	39
10/24/20	J. C., Jr.	61	

June 12, six days after ceasing to take thyroid, a rise to 21 had occurred.

June 14, the administration of pituitary was commenced, and a tracing taken July 2 showed the figure 36, practically a return to the normal for him.

Before commencing strychnin administration September 13, a tracing was taken September 12. The patient was feeling exceptionally well, and this was reflected in the number 39.

Strychnin was stopped September 20, and the following day the observation showed a drop to 26. Throughout the whole experiment, the dynamometer record has varied very little; the ergographic tracings have given much more valuable information, revealing variations in total work capacity rather than in degree of effort.

In considering the diagnosis of this condition, one is at once met with the striking absence of pathologic signs, except the infantile degree and character of muscular power; and the presence of creatin in the urine.

On clinical grounds, the varieties of progressive muscular atrophy are inadmissible, inasmuch as the condition is not progressive, nor is there evidence of muscular atrophy. Myasthenia gravis, amyotonia

congenita and pseudohypertrophic paralysis are mentioned merely to be dismissed.

What, then, is the condition? Is it a pathologic entity resulting from disease of or lack of development of some part of the nervous system, or some of the endocrine glands, or is it some inherent variation in muscle tissue? No support is given to the latter theory by histologic examination of muscle tissue. The solution of the mystery is closely bound up with the metabolism of creatin, regarding which many scattered pieces of evidence of variable trustworthiness are available, but regarding which no satisfactory evidence has been adduced of the source of supply or the mechanism of its transformation into creatinin. Creatin is normally present in young children and abnormally present in some pathological states. Why it should disappear as maturity is reached we do not know.

On the basis of clinical data, of ergograph and dynamometer records, and the presence of creatin in the urine, I venture to describe this as a case of muscular infantilism. Its ultimate cause is still unknown, and the condition is entirely uninfluenced as yet by treatment. Such observations as have been made tend to negative the suggestion that the endocrine glands are at fault.

ADMINISTRATION OF A PITUITARY EXTRACT AND HISTAMIN IN A CASE OF DIABETES INSIPIDUS *

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We have recently had the opportunity to study experimentally a rather severe case of diabetes insipidus. Our observations include the effect of lumbar puncture, the administration of pituitary extract hypodermically and by mouth, the effect of histamin injection, the nitrogenous metabolism before and as affected by pituitary extract, the blood constituents and the carbohydrate tolerance.

REPORT OF CASE

J. S., male, white, aged 24 years, single, a painter and mechanic, and an overseas man, was referred to the State University of Iowa Hospital, April 25, by Dr. F. H. Lamb of Davenport, Iowa, for chronic syphilis and polyuria.

Family History.—The family history was unimportant; the patient stated, however, that one brother is a great water drinker.

Present Illness.—The patient complained of loss of appetite, pain in the back and lower abdomen, occasional dimness of vision, dizziness, coldness and chills, polydipsia and polyuria, general weakness, and some loss in body weight (from 145 to 133 pounds). The syphilitic history dates from an exposure Sept. 15, 1915; sores developed on the penis and then in the throat in October following. He received some treatment at this time. In 1916, he had gonorrhea. In February, 1920, he was found to have a + + + + Wassermann reaction, and received some syphilitic treatment. A test made just before he entered this hospital was still + + + +, and another test after admission was + + +. It was difficult to get a statement as to the existence of a polyuria previous to the syphilitic infection, though that such may have obtained and become intensified subsequently is not excluded. The patient's trials in getting water to drink while a soldier in the front lines were particularly distressing.

Physical Examination.—Little of importance was found. There was no evidence of hypopituitary or hyperpituitary change.

Laboratory Examination.—The urine was free from protein and sugar. The blood gave 93 per cent. hemoglobin; 4,260,000 red cells and 7,200 leukocytes, with polymorphonuclears 72 per cent., lymphocytes 26 per cent., and eosinophils 2 per cent. Systolic blood pressure was 104 mm., diastolic 62 mm., and pulse pressure 42 mm.

The cerebrospinal fluid obtained May 1 by lumbar puncture was under no increased pressure; about 5 c.c. of clear fluid were drained. The Wassermann test was negative, Noguchi + +, and the fluid contained no cells.

The roentgenogram of the cranium shows a somewhat enlarged sella turcica with processes sharply defined. It is not to be regarded as abnormal.

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In Table 1 is given a summary of the twenty-four hour observations on the output and concentration of the urine during the period the patient was in the metabolism ward. On the first, sixth and seventh days, the nitrogen distribution in the urine was also determined. With the exception of the first day, the urine was collected hourly during the day, but the night urine (from 7 p. m. to 7 a. m. or from 8 p. m. to 8 a. m.) was mixed and measured in toto. Minimal and maximal specific gravities are therefore given. The nitrogen intake is calculated from the protein of the diet. The salt intake does not include the chlorid of the raw food, and, accordingly, a negative salt balance is shown. No salt was used in the preparation of the diet, but the patient was permitted salt ad libitum from a weighed container. The diet was essentially purin free and creatin free.

TABLE 1.—SUMMARY FOR TWENTY-FOUR-HOUR PERIODS

Day	Water Intake	Urine		Food N	Urine N		NaCl Intake	Urine NaCl		
		Volume	Sp. Gr.		Gm.	Per Cent.		Gm.	Per Cent.	
1	16,820	15,200	1.002	11.68	11.25	0.074	3.45	7.00	0.046	
2	15,370	16,800	1.001 1.002	12.16	9.95	0.060	4.78	6.76	0.040	
3	17,380	18,605	1.002 1.003	12.80	10.15	0.054	5.70	10.87	0.058	Lumbar puncture
4	25,000	19,075	1.002 1.003	12.64	9.02	0.047	8.21	8.83	0.046	
5	8,500	5,110	1.091 1.014	12.48	8.16	0.159	5.38	9.22	0.180	Pituitary extract hypodermically
6	4,120	4,190	1.002 1.013	17.12	7.74	0.185	14.81	3.25	0.077	Pituitary extract hypodermically
7	8,800	10,615	1.001 1.004	12.96	8.77	0.082	4.11	13.57	0.129	
8	9,060	11,975	1.001 1.008	13.12	9.46	0.079	11.61*	14.97	0.125	Histamin 0.2 mg. hypodermically
9	11,200	12,220	1.001 1.006	13.44	9.92	0.088	5.81	9.73	0.080	
10	.....	10,170	1.002 1.007	12.96	9.85	0.097	4.92	7.10	0.070	Dried gland by mouth
11	.....	10,365	1.002 1.005	12.00	8.88	0.085	4.49			
12	.....	9,100	1.002 1.006	10.56	7.74	0.085	4.42	4.57	0.050	Dried gland by mouth
13	.....	8,755	1.001 1.006	14.78	8.93	0.102	8.49	10.09	0.115	
14	.....	13,425	1.001 1.004	16.00	.....	.....	6.45			
15	.....	10,245	1.001 1.006	12.16	.....	.....	3.60	....	.....	Diarsenol
16	.....	9,020	1.991 1.004	11.20	.....	... .	5.24			
17	.....	9,405	1.002 1.004	11.52	.....	.....	3.20			
18	.....	10,385	1.002 1.006	10.08	.....	.....	5.04			
19	.....	11,940	1.002 1.005	.....	.....	.....	....	....	.....	Glucose tolerance and diarsenol

* Some sodium chlorid was taken by the patient in the afternoon "to relieve the headache."

The rather frequent association of polyuria with pathologic changes (e. g., basal syphilitic meningitis) which might affect the hypophysis through compression, suggests that the relief of pressure might be accomplished by spinal puncture. In a case reported by Herrick [1] the polyuria was relieved by lumbar puncture; the effect continued during

a month of observation. However, there was apparently no increased pressure of the cerebrospinal fluid and only 5 c.c. were removed. The effect was manifested on the day following the puncture and still more so on the third day. Berblinger [2] reported a case in which the volume of the urine was diminished following an operation for cerebral decompression. Graham [3] presents a case in which the relief of pressure (caused by traumatic injury) was immediately followed by the cessation of the polyuria and other symptoms. Fitz [4] found that the lumbar

TABLE 2.—Effects of Lumbar Puncture

Day & Hour	Volume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
8	810	1.002	0.080	0.648	0.074	0.595	
9	710	1.003	0.066	0.469	0.063	0.447	Lumber puncture
10	560	1.002	0.083	0.465	0.071	0.400	
11	900	1.002	0.066	0.594	0.050	0.447	
12	875	1.002	0.054	0.472	0.051	0.447	
1	800	1.002	0.046	0.396	0.052	0.445	
2	895	1.002	0.037	0.331	0.051	0.457	
3	800	1.002	0.046	0.392	0.052	0.445	
4	935	1.003	0.042	0.396	0.054	0.504	
5	875	1.002	0.040	0.350	0.050	0.441	
6	910	1.002	0.041	0.373	0.061	0.544	
7	850	1.002	0.040	0.340	0.048	0.410	
	10,040			5.223		5.592	
7-7	8,565	1.002	0.068	5.650	0.053	4.557	
Day 4							
8	940	1.002	0.080	0.752	0.048	0.454	
9	885	1.002	0.046	0.407	0.038	0.327	
10	700	1.002	0.044	0.333	0.037	0.282	
11	840	1.002	0.050	0.420	0.037	0.312	
12	885	1.002	0.050	0.443	0.050	0.446	
1	610	1.002	0.029	0.178	0.067	0.410	
2	845	1.003	0.034	0.287	0.053	0.444	
3	900	1.003	0.027	0.243	0.047	0.442	
4	895	1.002	0.029	0.260	0.045	0.403	
5	818	1.002	0.029	0.236	0.047	0.384	
6	900	1.002	0.034	0.306	0.053	0.479	
7	880	1.002	.....	.....	.....	.....	Specimen mixed in 7-7
	10,085						
7-7	8,990	1.002	0.050	4.940	0.047	4.634	Analyses include 7 p. m.

puncture was ineffective in his case, and Barker and Mosenthal [5] report likewise. In Williams' [6] case, some relief was obtained, but for the day following the puncture only.

In our case, the polyuria was not alleviated by spinal puncture. In fact the twenty-four hour output of urine on the day of the puncture and on the following day was actually increased over the preceding observations (Tables 1 and 2). Nor were there any particular changes in the amounts and concentrations of the hourly specimens.

1. Herrick, J. B.: Arch. Int. Med. **10**:1 (July) 1912.
2. Berblinger: Verhandl. d. deutsch. path. Gesell. **16**:273, 1913.
3. Graham, E. A: J. A. M. A. **69**:1498 (Nov. 3) 1917.
4. Fitz, R.: Arch. Int. Med. **14**:706 (Dec.) 1914.
5. Barker, L. F., and Mosenthal, H. O.: Tr. A. Am. Phys. **32**:233, 1917.
6. Williams, J. R.: Endocrinology **1**:312, 1917.

The subcutaneous injection of 1 c.c. of pituitary extract (Parke, Davis & Co., obstetrical pituitrin) resulted in a marked fall in the amount of urine secreted by our patient and an increase in the concentration. The maximum effect occurred during the third hour (Table 3, Day 5). A second injection early in the evening reduced the diuresis during the night. The administration of the pituitary extract at 8 a. m. the following morning brought the volume down to 37 c.c. for the fifth hour (Day 6). A final injection was given at 6 p. m. and was followed by an immediate fall to 55 c.c. for the succeeding hour. The 4,190 c.c. urine obtained this day indicate that the two injections per day were insufficient to control the diuresis completely.

TABLE 3.—Effects of Pituitary Extract Given Subcutaneously

Day 5 Hour	Volume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
9	815	1.001	0.075	0.611	0.045	0.367	
10	800	1.001	0.073	0.628	0.040	0.343	
11	725	1.001	0.088	0.638	0.045	0.326	1 c.c. pituitary extract at 10:20
12	75	1.012	0.552	0.414	0.553	0.415	
1	37	1.014	0.420	0.239	0.005	0.379	
2	92	1.007	0.340	0.313	0.406	0.374	
3	150	1.007	0.270	0.405	0.364	0.546	
4	273	1.004	0.185	0.506	0.193	0.527	
5	170	1.003	0.185	0.315	0.207	0.352	
6	235	1.004	0.165	0.388	0.180	0.423	
7	255	1.003	0.125	0.319	0.165	0.421	
8	260	1.004	0.190	0.494	0.260	0.706	1 c.c. pituitary extract at 7:30
	3,987			5.209		5.179	
8-8	1,145	1.006	0.300	3.435	0.241	2.757	

Each injection was followed by an immediate peripheral vasoconstriction and abdominal cramps. The patient's skin became moist. He could spit, and could swallow his food without washing it down with water as had been his custom. The intense thirst, general discomfort, pains in the back, etc., were immediately relieved. His appetite was marked, and more food was given him at his request on the second pituitrin day (Day 6). In addition to the large nitrogen intake, the greater voluntary consumption of salt on this day is of interest. The blood pressure was taken at 1 p. m. on the sixth day when the greatest antidiuretic effect was evident. The systolic pressure was 106 mm., diastolic 64 mm., and pulse pressure 42 mm.

The very positive but transient effects of pituitary extract injections are in accord with the findings reported in the literature.[7]

7. Von den Velden, R.: Berl. klin. Wchnschr. **50**:2083, 1913; Fermi, F.: Wien. klin. Wchnschr. **26**:1867, 1914; Römer, C.: Berl. klin. Wchnschr. **40**: 108, 1914; Hoppe-Seyler, G.: München. med. Wchnschr. **62**:1633, 1915; von Konshegg, A., and Schuster, E.: Deutsch. med. Wchnschr. **41**:191, 1916; Bab, H.: München. med. Wchnschr. **63**:1685, 1721, 1758, 1916; Rosenbloom, J.: J. A. M. A. **70**:1292 (May 4) 1918; Motzfeldt, K.: Boston M. & S. J. **174**: 644, 1916; Clausen, S. W.: Am. J. Dis. Child. **16**:195 (Sept.) 1918; Kennaway, E. L., and Mottram, J. C.: Quart. J. Med. **12**:226, 1919.

In connection with the questionable identification of histamin as the active principle of the posterior lobe of the hypophysis (Abel and Kubota [8]), it is of interest to note that tincture of ergot and "ergotin" have been used in the treatment of diabetes insipidus with some benefit (Futcher [9]). Again, Motzfeldt [10] found that a preparation of ergot had an inhibitory effect on diureses induced in rabbits, and he also obtained similar results with histamin and tyramin.

The administration of 0.2 mg. of histamin (Burroughs, Wellcome & Co.) has resulted in a definitely positive reduction of the volume and in an increased concentration of the urine (Table 4). As compared with pituitary extract, the results may be expressed relatively; while the pituitary extract increased the concentration of the sodium chlorid and the nitrogen of the urine six and fifteen times, respectively, the histamin effected a concentration of three and six times only.

TABLE 4.—Effects of Histamin Injection

Day & Hour	Volume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
9	480	1.001	0.092*	0.483*	0.057*	0.300*	
10	570	1.003	0.092*	0.483*	0.057*	0.300*	
11	350	1.003	0.112	0.392	0.098	0.343	Histamin 0.2 mg. at 10:20
12	105	1.008	0.320	0.336	0.372	0.391	
1	300	1.002	0.090	0.270	0.124	0.370	
2	710	1.001	0.080*	0.532*	0.087*	0.577*	
3	620	1.002	0.080*	0.532*	0.087*	0.577*	
4	420	1.002	0.144*	0.669*	0.101*	0.469*	
5	510	1.002	0.144*	0.669*	0.101*	0.469*	
6	480	1.003	0.136*	0.925*	0.070*	0.479*	
7	680	1.002	0.136*	0.925*	0.070*	0.479*	
7-7	5,980	1.003	0.136	8.133	0.073	4.353	
8	580	1.004	0.108	0.626	0.061	0.356	
	11,985			14.976		9.465	

* Average per hour for 2 hour period.

A general peripheral vasodilation immediately followed the injection; the subsequent severe headache and general prostration lasting until evening are seemingly characteristic of histamin (Popielski [11]) and are widely variant from the effects of the pituitary extract. The administration of the histamin caused so much discomfort to the patient that the experiment was not repeated.

8. Abel, J. J., and Kubota, S.: J. Pharmacol. & Exper. Therap. **13**:243, 1919; Dudley, H. W.: ibid. **14**:295, 1919; Jackson, D. E., and Mills, C. A.: Lab. & Clin. M. **5**:1, 1919; Hanke, M. T., and Koessler, K. K.: J. Biol. Chem. **43**:557, 1920.

9. Futcher, T. B.: Tr. A. Am. Phys. **19**:247, 1904.

10. Motzfeldt, K.: J. Exper. M. **25**:153, 1917.

11. Popielski, L.: Arch. f. d. ges. Physiol. (Pflüger) **178**:237, 1920.

The results are interpreted as indicating that histamin is not the active principle of the pituitary gland. However, the antidiuretic substance is probably some related compound, as suggested by Kennaway and Mottram. We understand that Rowntree has failed to duplicate the action of pituitary extracts in diabetes insipidus by injections of histamin.

TABLE 5.—Effects of Dried Whole Gland Given by Mouth

Day 10 Hour	Volume	Sp. Gr.	NaCl		N		
			Per Cent.	Gm.	Per Cent.	Gm.	
9	360	1.004	0.088	0.317	0.079	0.285	
10	500	1.008	0.088	0.519	0.097	0.584	
11	540	1.002	0.080	0.432	0.088	0.473	Dried gland, 3 grains by mouth
12	270	1.005	0.080	0.216	0.160	0.432	Dried gland, 3 grains by mouth
1	500	1.002	0.056	0.280	0.115	0.575	
2	360	1.004	0.056	0.202	0.094	0.338	Dried gland, 3 grains by mouth
3	710	1.002	0.048	0.341	0.096	0.684	Dried gland, 3 grains by mouth
4	165	1.007	0.150	0.248	0.220	0.362	
5	320	1.004	0.068	0.282	0.136	0.445	
6	120	1.007	0.104	0.125	0.253	0.304	
7	405	1.008	0.060	0.308	0.114	0.462	
7-7	5,470	1.002	0.068	3.720	0.084	4.595	
8	360	1.004	0.060	0.216	0.088	0.315	
	10,170			7.101		9.852	
Day 11							
8-10	820	1.002	0.048	0.394	0.072	0.587	
11	615	1.002	0.080	0.492	0.072	0.443	
12	350	1.004	0.092	0.322	0.095	0.331	
1	345	1.008	0.080	0.276	0.097	0.333	
2	520	1.008	0.080	0.416	0.085	0.444	
3	745	1.002	0.056	0.417	0.082	0.608	
4	465	1.002	0.066	0.307	0.092	0.430	
5	575	1.002	0.080	0.460	0.089	0.511	
6	285	1.004	0.090	0.151	0.116	0.331	
7	465	1.008	0.052	0.242	0.130	0.592	
7-7	4,850	1.008	.....	.....	0.084	3.874	
8	330	1.005	0.160	0.528	0.120	0.396	
	10,365					8.880	

Essentially negative results are reported throughout the literature as the result of administering pituitary preparations by mouth in diabetes insipidus. Barker and Mosenthal state that the administration of the extract of the posterior lobe by mouth in tablet form, even in fairly large doses, did not prove to be of value. Motzfeldt, however, was able to check the diuresis in one case by feeding the fresh posterior lobe of the ox. Kennaway and Mottram gave 1 c.c. of pituitary extract by mouth twice daily over a period of eight days with no appreciable lessening of the polyuria.

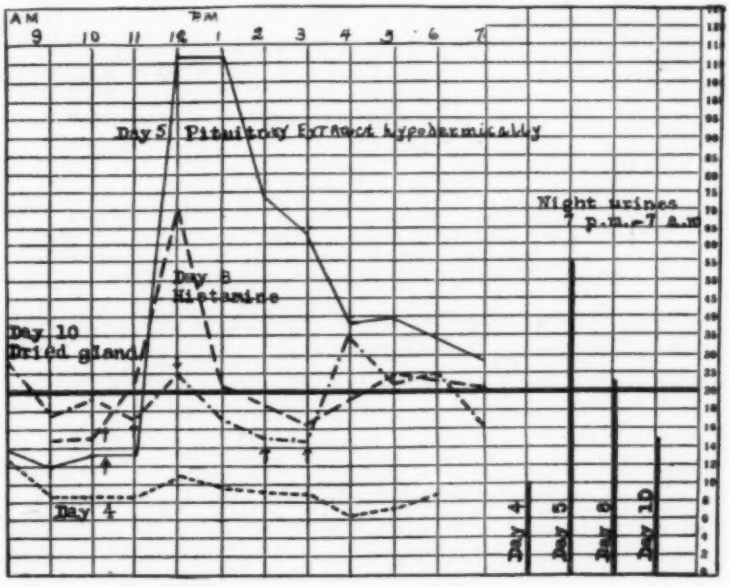
It is probable that the active substance of the posterior lobe of the hypophysis is destroyed in the alimentary tract. Thus, while Dale [12] failed to alter the activity of the extract of the gland by peptic diges-

12. Dale, H. H.: Biochem. J. **4**:427, 1909.

tion in 0.2 per cent. hydrochloric acid for twenty-four hours, every active preparation of trypsin tried reduced the effects on blood pressure and urinary flow (Schäfer) practically to *nil* after a few hours.

There is a definitely diminished volume and increased concentration of the urine collected hourly as the result of giving by mouth comparatively large amounts of the dried whole gland (Table 5, Day 10), though the effect is not great. The continued administration by mouth of the dried whole gland (25 grains) over a twenty-four hour period on the twelfth day was hardly more favorable.

It is of interest to note that following the first subcutaneous injection of pituitary extract, the daily output of urine fell from over 15,000



Diabetes insipidus: hourly urine concentrations. The sum of the sodium and chlorin percentages are plotted as decigrams per 100 c.c. of urine.

c.c. to about 10,000 c.c., and the concentration relatively increased. There is undoubtedly a slight beneficial effect which persists for some days after pituitrin administration. That this may be manifest when pituitary preparations are given by mouth is indicated; exclusive of the days when pituitary extract was given subcutaneously, the least twenty-four hour elimination occurs on the thirteenth day.

Kennaway and Mottram conclude that the sum of the nitrogen and chlorin percentages in the urine must be proportional to a very large

fraction of the total urinary solids, since the sulphates, and in part the phosphates (as products of protein metabolism), will vary in the same manner as the nitrogen. Their curve shows a very close parallelism between the Δ of the daily urines and the nitrogen plus chlorin in grams per cent. "When large amounts of sodium chlorid are given, the diuresis is so adjusted that the percentage of nitrogen plus chlorin in the urine remains unaltered."

Hourly concentration curves of the twenty-four hour urines of our case show this same constancy during the day except for a relatively greater concentrating power in the early morning hour, as shown in the accompanying illustration. The comparative effects of pituitary extract and histamin on the power of the kidneys to concentrate are brought out in a striking manner.

TABLE 6.—NITROGEN PARTITION AND EFFECTS OF PITUITARY INJECTION

Day	Food N, Gm.	Total N, Gm.	Urea N		Ammonia N		Uric Acid N		Creatinin N		Undetermined N	
			Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.	Gm.	Per Cent.
1	11.68	11.25	7.69	68.4	0.84	7.5	0.22	1.9	0.51	4.5	2.00	17.8
6	17.12	7.74	5.60	72.2	0.71	9.2	0.29	3.8	0.48	5.2	0.67	8.6
7	12.06	8.77	5.75	65.7	0.94	10.7	0.20	2.2	0.50	5.7	1.38	15.7

Pituitary extract injections, two doses, 1 c.c. each, were given Day 6.

Figures for the composition of the urine in diabetes insipidus are limited chiefly to the determination of total nitrogen and sodium chlorid as evidence of the concentrating power of the kidneys. The results for total nitrogen have been essentially normal. Hawk [13] has shown that the consumption of large amounts of water affects the nitrogen metabolism in normal persons; similar changes, at least, might be expected in diabetes insipidus. Table 6, Day 1, shows that high total nitrogen, ammonia nitrogen, and undetermined nitrogen figures obtain. A lessened elimination and a considerable retention of nitrogen occurred on the sixth day, the second pituitary extract day; the nitrogen partition on this day is more normal in character. On the post-pituitary extract day (Day 7), there was a tendency to revert to the picture for the first day. The first pituitary extract day (Table 1, Day 5) shows a low total nitrogen also. There was no creatinuria. Uric acid is rather high for a nonpurin diet, and is increased on the pituitary extract day despite the diminished water excretion.

Rosenbloom and Price [14] reported figures for the nitrogenous and mineral metabolism in a boy with diabetes insipidus.

13. Hawk, P. B.: Biochem. Bull. **3**:420, 1914.
14. Rosenbloom, J., and Price, H. T.: Am. J. Dis. Child. **12**:53 (July) 1916.

The figures obtained for the several blood constituents are given in Table 7.

There is hypoglycemia and a high uric acid content. Other constituents are normal.

Very high blood uric acid figures are reported by Hammett, Patten, and Suitsu [16] as a physiologic reaction to pituitary extract administration in nonendocrine cases. Socin and others have found that the Δ and the sodium chlorid content of the blood serum are essentially normal in diabetes insipidus. Williams reports high blood fat and blood cholesterol in his case.

Blood glucose determinations (Benedict) on the nineteenth day before and two hours after the ingestion of 100 gm. glucose were 0.093 and 0.092 per cent., respectively; with the modified method (Table 7, note), the figures were 0.073 and 0.064 per cent, respectively. Urine specimens collected hourly were negative for sugar (Fehling).

TABLE 7.—Composition of the Blood (Subsequent to Pituitrin Administration)

	Day 15	Day 17	Day 20
Urea nitrogen	9.1 mg.	11.9 mg.	
Creatinin	0.6 mg.		
Uric acid	4.0 mg.	7.4 mg.	3.0 mg.
Plasma sodium chlorid*	64.4 mg.		
Glucose (Benedict), per cent.	0.079		
Glucose (modified Benedict)†	0.041		
Plasma proteins, per cent.	6.06		

* 4 c.c. plasma, 10 c.c. water, and 7 c.c. saturated iron alum solution made up to 25 c.c., and heated in the boiling water bath. The precipitated proteins were filtered off. To the filtrate (17.5 c.c.), 2.5 c.c. of standard silver nitrate solution (Volhard-Arnold) and two drops of concentrated nitric acid were added, and 15 c.c. of this filtrate were titrated with the standard thiocyanate solution 5-fold diluted. The sample was not collected under paraffin oil.[15]

† After adding 0.25 c.c. of dilute sulphuric acid to the blood before precipitating with the sodium picrate-picric acid reagent, and using 1.1 c.c. of sodium carbonate solution for the reduction.

Sugar tolerance tests have been employed by Römer, Motzfeldt, Richter [17] and Schnabel and Gerhard.[18] A normal or increased tolerance is indicated by these observations.

The patient did not remain in the hospital long enough for a more complete study or for additional and satisfactory syphilitic treatment. But two injections of the diarsenol brand of arsphenamin were given, one the day previous to leaving the hospital. Indirect word was received from the patient subsequently that no relief from the polyuria had obtained.

15. Myers, V. C., and Short, J. J.: J. Biol. Chem. **44**:47, 1920.
16. Hammett, F. S.; Patten, C. A., and Suitsu, N.: Am. J. Physiol. **41**: 588, 1920.
17. Richter, G. J.: J. Missouri M. A. **13**:308, 1916.
18. Schnabel, T. G., and Gerhard, A. M.: New York M. J. **111**:812, 1920.

Contrary to earlier opinions, Elsner [19] states that he has not been able to control the complex in these cases by specific treatment. Römer and also Fitz report that syphilitic treatment had no noticeable effects in their respective cases.

SUMMARY AND CONCLUSIONS

A severe case of diabetes insipidus with chronic syphilis was studied.

The symptoms were not relieved by lumbar puncture.

The subcutaneous administration of pituitary extract (doses, 1 c.c. each, of the obstetrical preparation) was effective temporarily in increasing the concentration and reducing the volume of the urine, as reported by other observers. A normal twenty-four hour volume and concentration were not obtained.

Histamin (1 injection of 0.2 mg.) gave a similar but less effective result. It is probably not the active principle of the pituitary gland.

Desiccated whole pituitary substance in four 3 grains doses by mouth had a slight immediate effect.

On the day following the first injections of the pituitary extract and on subsequent and intervening nonpituitary extract days, there was a maintained decrease in the polyuria from over 15 liters to about 10 liters per day and a relative increase in the concentration of the urine.

Nitrogenous metabolism (over twenty-four hour periods) is affected in part as in the case of a normal person with a large water intake (Hawk). High ammonia, uric acid, and particularly undetermined nitrogen figures, were obtained; there was no creatinuria. As the result of pituitary extract injections, there was a lower nitrogen elimination with considerable retention, diminished ammonia and undetermined nitrogen, and a somewhat increased uric acid output; the nitrogen partition was more nearly normal.

Glycogenesis was not reduced. There was hypoglycemia. Blood urea, creatinin, plasma chlorids, and total plasma proteins were normal. The very high blood uric acid figures obtained may be explained as an effect similar to that of pituitary extract administration in nonendocrine cases.

We wish to thank Dr. F. H. Lamb of Davenport, Iowa, by whom the case was referred to Dr. C. P. Howard for study. The diets were calculated and prepared by Miss Gertrude Whiteford.

19. Elsner, H. L.: Monographic Medicine **4**:1123, 1916.

INFLUENZA PANDEMICS DEPEND ON CERTAIN ANTICYCLONIC WEATHER CONDITIONS FOR THEIR DEVELOPMENT

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SYNOPSIS

Air pressure records (1826-1920) exhibit the fact that high pressure periods, lasting a number of years, vary with similar periods of low air pressure. Changes in solar activity harmonize with and apparently cause such pressure periods. Influenza pandemics and pneumonia epidemics develop only during high pressure periods. Influenza pandemics of 1890, 1891, 1918, 1919 and 1920 prove this fact as far as records are obtainable for the Northern Hemisphere and probably also for the Southern Hemisphere. All these epidemics come to a more or less sudden end following the advent of distinctly low air pressure. Records of cities in a highly diversified climate, as, for instance, California represents, prove that no meteorologic element, except air pressure, runs parallel to the development of influenza or pneumonia epidemics. Since it is definitely proven that these epidemics are a function of anticyclonic weather values, we must extend our laboratory work to an investigation of the physics of the atmosphere. The proposition is, whether the atmosphere during those epidemics acts as the carrier of a certain virus, or whether its physicochemical quality, changed during such weather periods, is the cause of influenza.

* * * *

The relation of climate or weather to health, and especially to the incidence of pneumonia and influenza epidemics, always has been a most difficult problem for the investigator. The people living on the continents experience a climate which changes almost hourly in temperature, humility and other meteorologic elements. There is a constant movement of the air that surrounds us. On the continent of Europe and on the area of the United States the air is generally moving from the West to the East. This movement is subject to a change in its direction; for instance, by the occasional influx of gigantic masses of air, generally coming from a northerly direction, but also descending from considerable height. Such inflowing air may cover the entire continents and assemble there for a number of weeks, without any tendency to resume the easterly direction. As increase of air pressure is necessarily incidental to such air assemblage, and as the mechanical effect of such pressure has been considered negligible, the influence on health of this meteorologic factor has been generally disregarded in favor of tem-

perature and humidity as the principal factors affecting health. If we scrutinize the foundation for the latter assumption on areas of the continents which are not subject to any material change of temperature and humidity from summer to winter, as for instance, on the coast area of California, from San Francisco to San Diego, it becomes clear that the so-called "cold weather diseases" or respiratory diseases are not a function of temperature and humidity, but are dependent on certain high air pressure conditions. This fact, abundantly proven on such areas,[1] eliminates temperature and humidity as important factors. As humidity has lately been put into the foreground as a more important factor than temperature, it is of special interest that in such parts of the continents where humidity is very low we find exactly the same development of "respiratory diseases" as on very humid areas. For instance, the incidence of pneumonia epidemics in concentration camps of the U. S. Army from 1917 to 1919 proved that camps with a monthly relative humidity of below 50 per cent. had the same incidence as camps with a relative humidity above 80 per cent.; that camps in Southern California and Texas, with a maximum of sunshine, had the same incidence as those on the Atlantic coast. However, all of the camps in the United States were subject to the incidence of pneumonia epidemics, whenever they happened to be under the influence of certain high air pressure conditions.

Since the appearance of the influenza pandemic of 1889, we have had a number of references in literature[2] to the appearance of high pressure periods simultaneously with the outbreak of influenza. A study of such periods became imperative. Anticyclones are formed in the rear of extensive cyclones by the discharge of immense, cold masses of air into lower latitudes.[3] An area of high pressure results. If the cyclone ahead of this area retards its procession, then a more or less stationary anticyclone is formed. In its center the air is descending by gyration and flowing outward everywhere in its circumference. Its rate of progress is about 41 kilometers per hour in the United States and 25 kilometers in Europe (46 kilometers for the cyclones). Such an anticyclone may remain stationary, however, for from one to four weeks over the entire United States, or the entire area of Europe. Differing from these originally cold anticyclones there appear sometimes others of likewise long duration, which are dynamically warm from the beginning, and which appear to have their origin in the upper circulation of the atmosphere. They are of rather rare occurrence and extend probably into the substratosphere (from 5 to

1. Richter, C. M.: J. A. M. A. **36**:188 (Aug. 4) 1894.
2. Richter, C. M.: J. A. M. A. **51**:660 (Aug. 22) 1908; **57**:1964, (Dec. 16) 1911; Anders, H. S.: Philadelphia M. J., Jan. 24, 1903.
3. Hann, J.: Lehrb. der Meteorologie, 1915, p. 624.

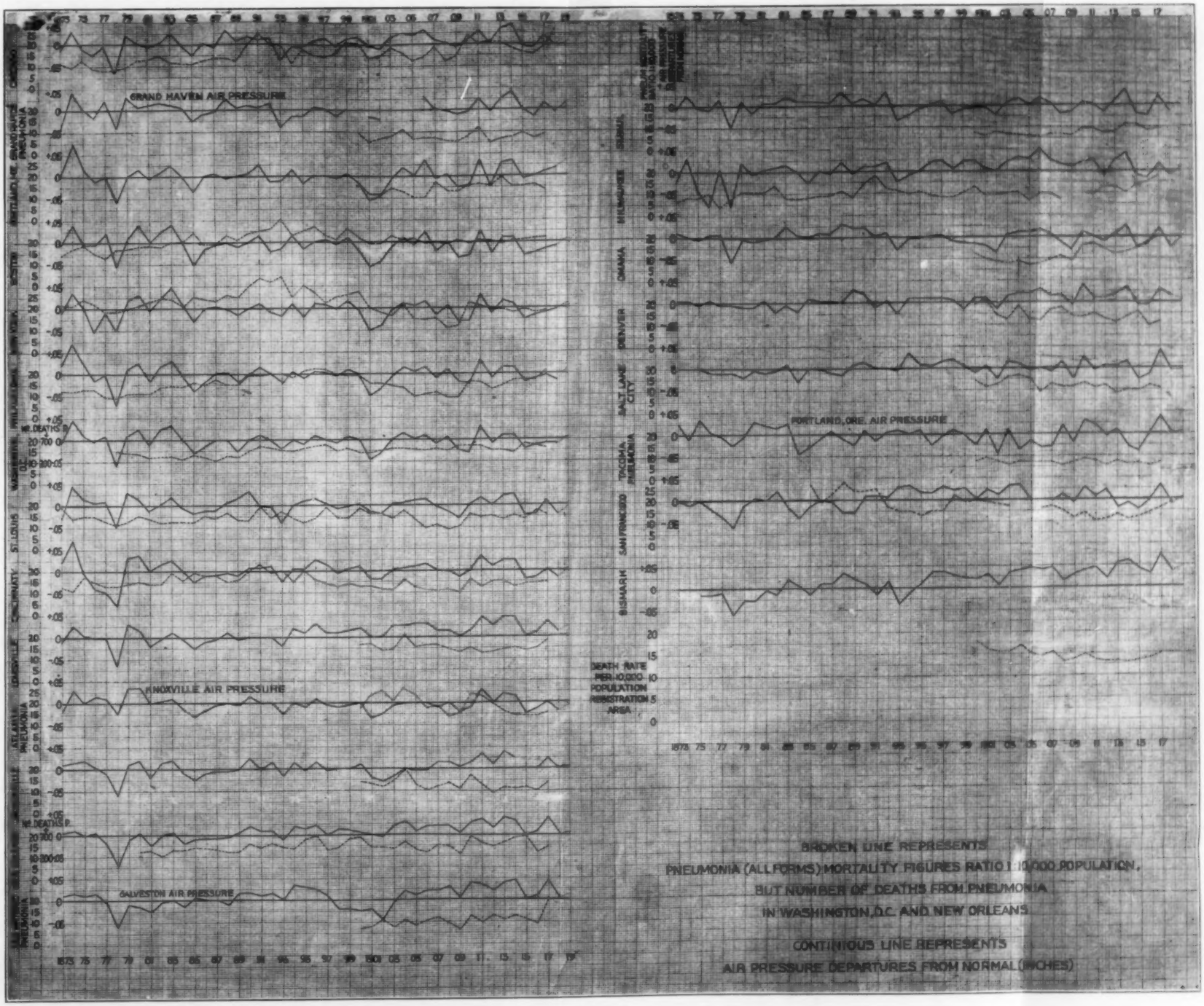
GRAND HAVEN AIR PRESSURE
KNOXVILLE AIR PRESSURE
GALVESTON AIR PRESSURE
PORTLAND, ORE. AIR PRESSURE
BROKEN LINE REPRESENTS
PNEUMONIA (ALL FORMS) MORTALITY FIGURES RATIO 1:10,000 POPULATION,
BUT NUMBER OF DEATHS FROM PNEUMONIA
IN WASHINGTON, D.C. AND NEW ORLEANS
CONTINUOUS LINE REPRESENTS
AIR PRESSURE DEPARTURES FROM NORMAL (INCHES)

Figure 1

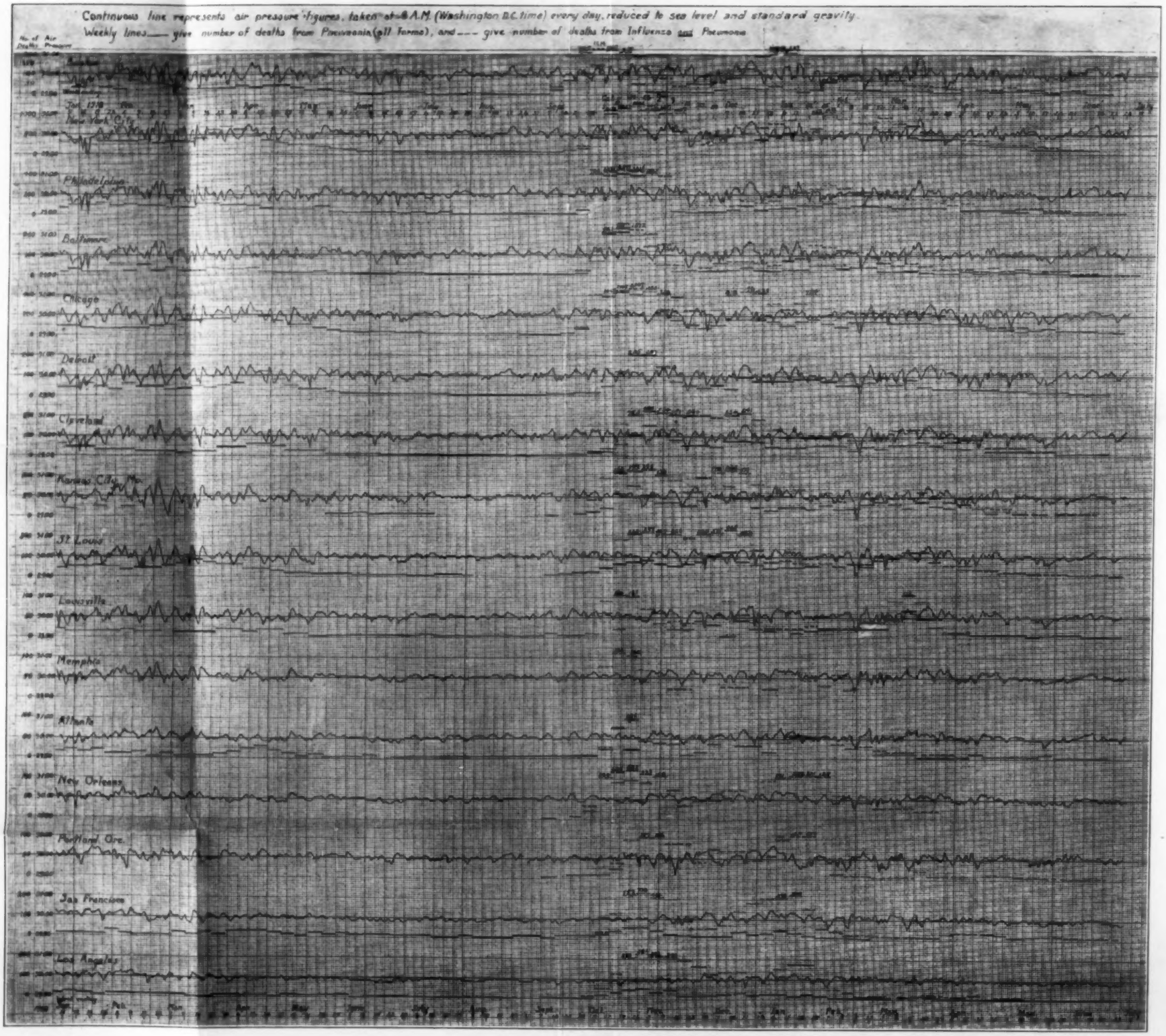
Continuous line represents air pressure figures, taken at 8 A.M. (Washington D.C. time) every day, reduced to sea level and standard gravity.
Weekly lines —— give number of deaths from Pneumonia (all forms), and - - - - give number of deaths from Influenza and Pneumonia
No. of Air Deaths Pressure
Boston
New York City
Philadelphia
Baltimore
Chicago
Detroit
Cleveland
Kansas City, Mo.
St Louis
Louisville
Memphis
Atlanta
New Orleans
Portland, Ore.
San Francisco
Los Angeles

Figure 2

9 kilometers). (The so-called troposphere extends from about 1 to 5 kilometers, and the stratosphere from 9 to 15 or more kilometers).

Our weather conditions do not depend, in reality, on cyclones and anticyclones, but on the great air currents in the substratosphere, which determine the dynamics of the atmosphere.[4] The entire weather system of the United States, for instance, according to Bigelow,[5] varies systematically with the variation of sun protuberances and sun spots. An increase of solar activity brings the cyclones into lower latitudes, increases the east drift of the upper air currents, lowers the temperature and increases the air pressure (lowers it at the equator). Koppen [6] declares that we possess in the eleven year sun-spot period the first directly proven period of weather conditions, even if not parallel to year or day. Naturally, this eleven year period must also be in direct relation to air pressure variations on our continent. Nansen [7] summarizes thus: In different groups of areas on the earth the meteorologic elements (temperature, rainfall, barometric pressure, etc.) fluctuate, or pulsate, so to speak, in time with one another, while in other groups of areas the fluctuations or pulsations are exactly inverted, and finally some areas show transition stages between the two. The result of all this is a very complicated picture of the meteorologic fluctuations. But by means of appropriate analysis we see that from this complicated and apparently chaotic set of fluctuations there arises a clear picture of the very intimate relation between all these variations, and the variations in the sun's activity. We have seen that even changes of very short duration in the sun's radiation (of heat as well as electricity) are distinctly repeated in our meteorologic conditions. The effects of the solar variations are probably transferred by means of variations produced in the distribution of pressure in our atmosphere. Changes in solar radiation probably first affect the higher layers of our atmosphere and thus create an unrest, which in turn is transmitted to the lower strata near the earth's surface. Such dynamic changes will produce different effects in different regions of the earth. Richter [8] demonstrated in 1892 this correlation of air pressure and sun-spot periods.

Anticyclones in the United States present four types: [9]

1. Appearing off the Pacific coast,[10] generally spring and fall; (a) off the coast of Washington and Oregon; (b) off the coast of California.

2. Alberta type (Southwestern Canada) west of the hundredth meridian.

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4. Shaw, W. H.: Meteorolog. Ztschr., 1914, p. 67.
5. Bigelow, F. H.: Am. J. Sc., August, 1910.
6. Koppen, W.: Meteorolog. Ztschr., 1914, p. 327.
7. Nansen, F.: J. Washington Acad. Sc., March 4, 1918.
8. Richter, C. M.: Meteorolog. Ztschr., August, 1892.
9. Bowie, E. H., and Weightman, R. H.: Monthly Weather Rev., Supplement 4, 1917.
10. De C. Ward, R.: Ann. Assn. Am. Geographers **4**: 1915.

3. Rocky Mountains—Plateau Region type.

4. Hudson Bay Type, east of the hundredth meridian, region of the Great Lakes.

During the years 1892 to 1912 (inclusive) 1,937 anticyclones and 2,597 cyclones entered the United States.

The following figures give the number of the different anticyclonic types registered during this period:

1. (a) North Pacific, 383.16; (b) South Pacific (California), 192.
2. Alberta, 947.
3. Plateau and Rocky Mountain Regions, 272.
4. Hudson Bay, 143.

Their average speed of progression was 22.7 miles per hour. "These anticyclones generally move east by south, whilst the cyclones move east by north inside the United States. The frequency of anticyclones is greatest in January and least in June. The Alberta Highs not infrequently in the winter months move almost due south to the West Gulf states." [9] As we see, nearly all of the anticyclones appear north of latitude 46° and west of the hundredth meridian. "Of 81 anticyclones of more than 787 mm. (31"), in America and Europe-Asia (1877-1844) one appeared in October, 8 in November, 34 in December, 29 in January, 4 in February and 5 in March." [8]

In Europe four types are recognized.[11] They are called according to origin:

1. Spanish.
2. Russian-Scandinavian.
3. Central European.
4. Iceland.

The Spanish anticyclone is part of the constant subtropical Atlantic Ocean High, central over the Azores. It extends northerly in summer, sometimes as far as Iceland, but its branches at other times reach Scandinavia on their path across continental Europe. The Azores High in some years may extend easterly to such an extent that one of the great, stable, dynamic Highs is created, locating over the area of Europe for many weeks. The Russian-Scandinavian Highs are typical continental anticyclones, having their nucleus in Siberia, Turkestan or China. Air pressure inside their area may reach 800 mm., while the Spanish type may reach 775 mm. The Iceland Highs probably originate in Greenland, while the Central European Highs appear to be parts of the Russian or Azores Highs.

In an extensive air pressure study, covering the years 1826 to 1885, Hann [12] demonstrates that periods of very high air pressure

11. Dreis, J.: Meteorolog. Ztschr., Feb. 1, 1915.
12. Hann, J.: Die Vertheilung des Luftdrucks über Mittel- u. Süd Europa, Wien., 1887, p. 110.

appear only at great intervals. Such a period existed from 1832 to 1836 in Middle Europe, extending from Petersburg to Warsaw, to Hungary, Paris, Basel and Palermo. It was a period of enormously high pressure, not equaled again before 1885. However, Petersburg had very high pressure again in 1839 and 1840. Another fact elucidated by Hann was the existence of a period of distinctly low pressure extending from Warsaw to Palermo from 1851 to 1855. A long period of high pressure followed from 1856 to 1864. The years 1874 to 1878 represented a low pressure period. We have no reliable pressure data for the United States before 1873. It appeared to Hann that the maximum pressure progressed from North to South. Hann's table also suggests that the years from 1842 to 1847 were a low pressure period; from 1847 to 1851 being a higher pressure period, and an increasing pressure after 1880. Hann notes the existence of a continuous rise of pressure during January in all years from 1826 to 1885, while pressure during April declined. He finds that deviations of pressure from normal have the same intensity and the same general character over the entire area of Europe.

The same fact is exemplified over the area of the United States. It has been made a special study by F. H. Bigelow,[13] who found that:

> The secular variations of the barometer from year to year are by no means accidental, but a phenomenon of definite proportions. The years of maximum pressure (over the United States) are 1874-75, 1882-83, 1890, 1896-97 and those of minimum pressure are 1878, 1884-85, 1893, with an interval of about eight years each. The years of depression seem to have a wider amplitude than the years of maximum. Between the successive large minima there is usually a large maximum broken in two parts by a minor minimum, as in 1876, 1881, 1889, 1895. These minor depressions are not so persistent throughout the entire United States as the strong minima, and in fact some years there seems to exist a powerful and persistent directive impulse, that really dominates the prevailing pressure. In seeking the causes of this phenomenon, one may suspect purely cosmical causes due to the variable solar output; indeed, these barometric variations do closely follow the variations in the sunspot frequency and the other products of the sun's variable activity. It is evident that we can now correlate the years which have similar secular variations and study them climatologically to see if there are any marked and prevailing features which characterize them.

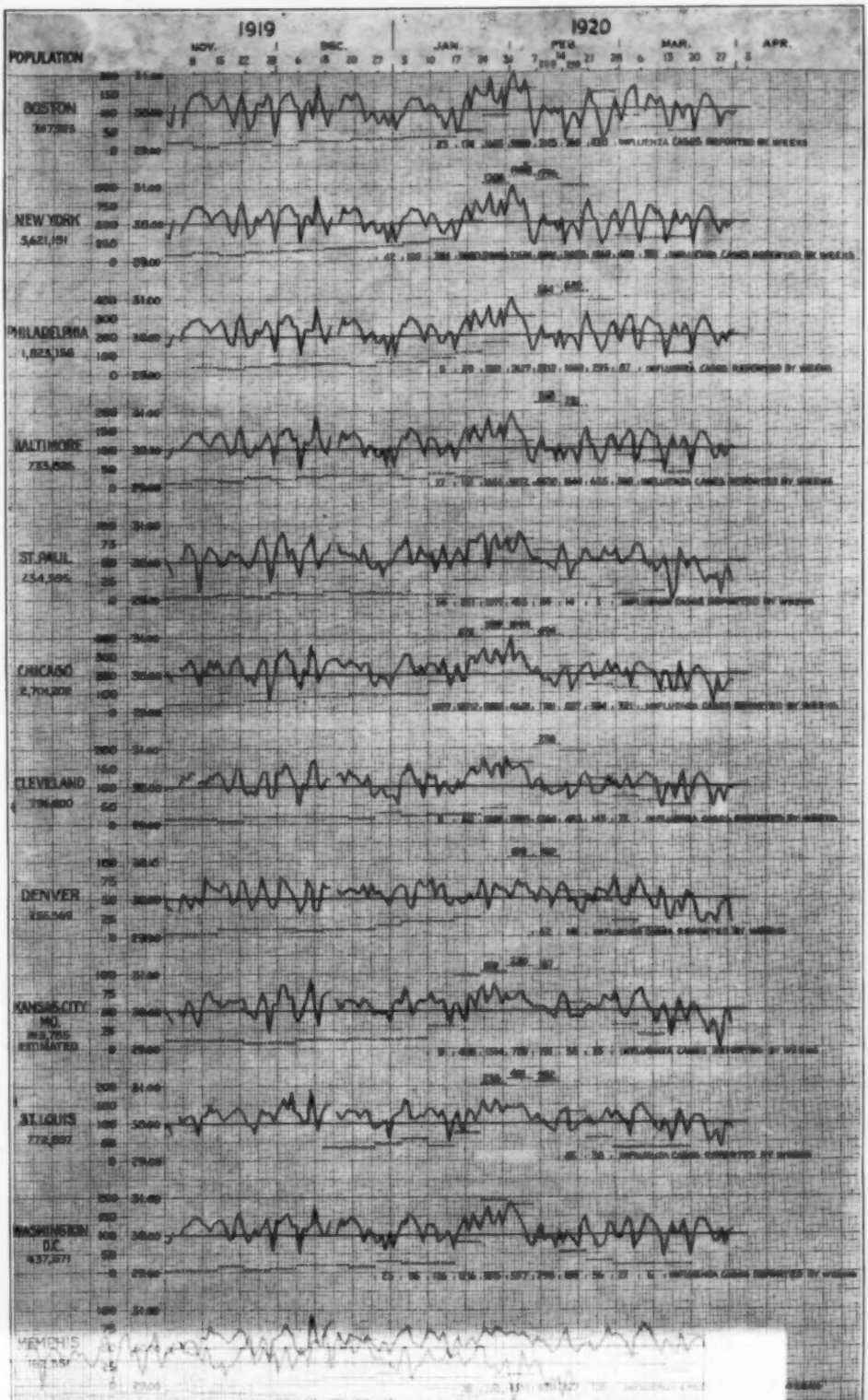
Bigelow's study embraces the years from 1873 to 1899. Since then years of minimum pressure have been 1901, 1902, 1909 and 1915 with minor minima in 1905, 1907 and 1912. The maximum pressure years extend continually from 1903 to 1908 and then from 1910 to the beginning of 1915. The last increase begins at the end of 1917 and extends into 1920. The North Dakota Station, Bismarck, seems to act as the key to this long series of high pressure years, showing a rise of pressure from 1878 to 1919. It is the gate for the Alberta

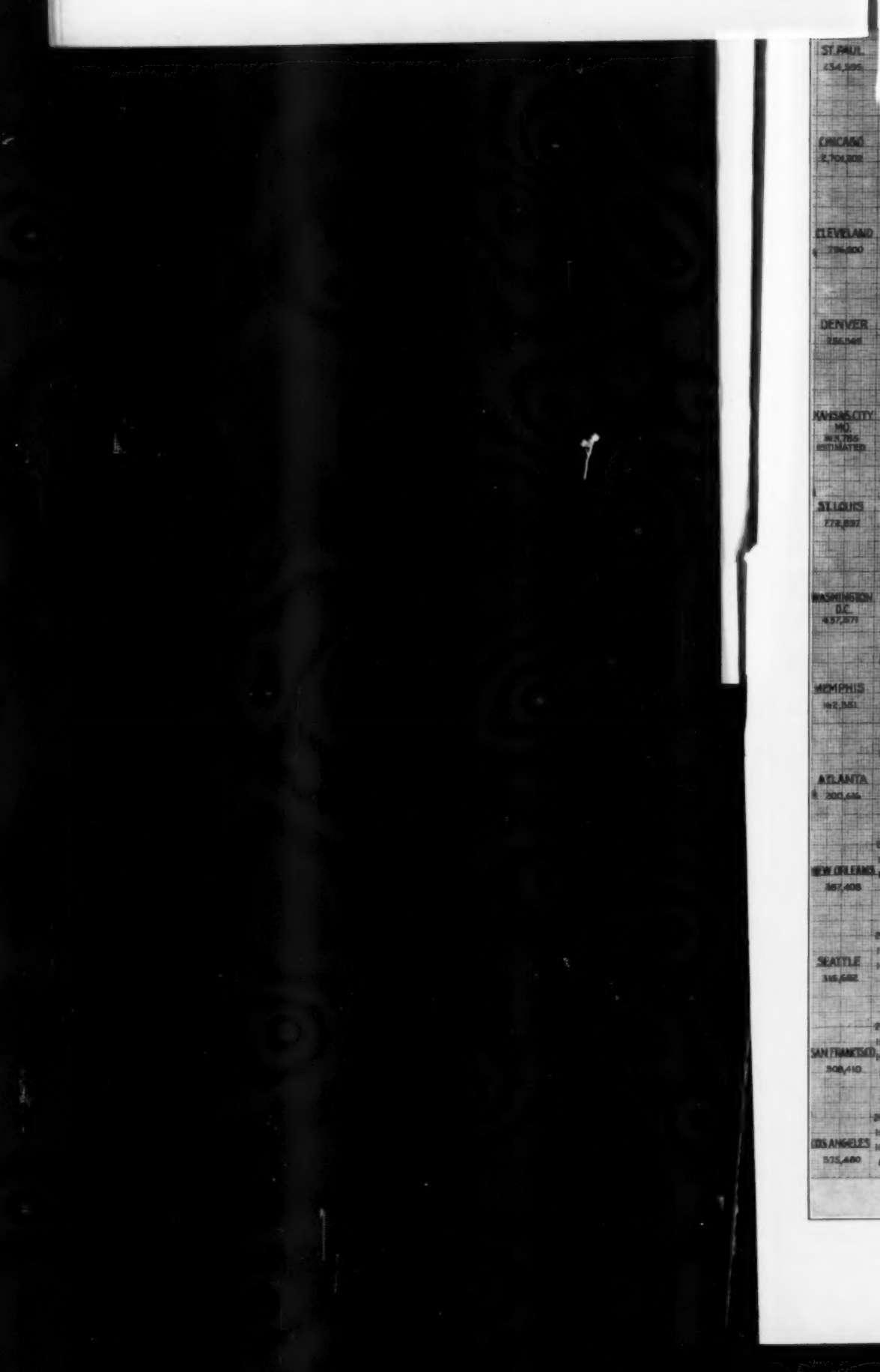
13. Bigelow, F. H.: Rept. Chief of Weather Bureau **2**: 1900, 1901.

Highs which enter the United States in that region and then sweep over the United States in a southerly and southeasterly direction. Figure 1 shows, in accordance with Bigelow's findings, that certain years of minimum or maximum pressure are very clearly indicated by each station of the chart, most conspicuously for 1878. As Bigelow remarks: "The residuals of that year are persistently minus, 0.05 inch, for each station of the United States: for 1883 they are persistently plus, about 0.02 inch. This means a relative reduction, or increase of air pressure, representing a weight of many million tons of air covering the United States."

If we follow the pneumonia mortality line in Figure 1 we are struck at once by the remarkable fact that the period of low pressure from 1875 to 1879 corresponds with a well marked trough in the mortality curve. The low pressure period from 1884 to 1885 also harmonizes well with a diminished pneumonia mortality. The 1893 Lows are generally followed by the mortality line in the same, or the following year. There is very well marked harmony between the two curves during the "Low" period of 1901-1902, likewise in 1909 and 1915. These are the principal "Low" periods. The United States curve also indicates low mortality during 1901-1902, in 1908-1909 and in 1914. It also gives an intermediate depression in 1905, which is likewise clearly indicated in the air pressure Low.

The principal air pressure maximum period in 1874-1875 harmonizes with the mortality peak in 1875. The general air pressure rise in 1879 is followed by the general rise of mortality, and both curves extend with this character during the High of 1882-1883. An irregular rise of both curves follows with an intermediate common peak at 1888. A more definite period of high pressure begins at 1890—the beginning pandemic—with peaks common also to the pneumonia mortality in 1890, 1891, 1893, 1895, 1896, 1897, 1899 and 1900, when the Low period appears. The general rise of pressure from 1903 to 1908 exhibits a greater common rise in 1903, still more in 1904, in 1907 and after the Low of 1908-1809 in 1910-1911. A following High period from 1911 to 1915, has common peaks at all cities, although of an irregular type. The United States curve has well outstanding peaks at 1900, 1904 and 1907. After 1915 we notice a general rise of both curves leading into 1918, when the new pandemic begins at the second half of that year, following a period of unusually low pressure at the beginning of 1918, which is for this reason only not accompanied by a distinctly high pressure line for that year. The United States curve likewise rises clearly since 1915. It is obvious, that any conclusions that might be formed from this chart, may have to be qualified in regard to the accuracy of the mortality statistics. We may accept the.


1919
1920
POPULATION
NOV.
DEC.
JAN.
FEB.
MAR.
APR.
BOSTON
NEW YORK
5,621,151
PHILADELPHIA
1,823,158
BALTIMORE
733,826
ST. PAUL
234,595
CHICAGO
2,701,205
CLEVELAND
796,800
DENVER
256,369
KANSAS CITY MO.
ESTIMATED
ST. LOUIS
772,897
WASHINGTON D.C.
437,571
MEMPHIS


ST. PAUL
CHICAGO
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ATLANTA
NEW ORLEANS
SEATTLE
SAN FRANCISCO
LOS ANGELES

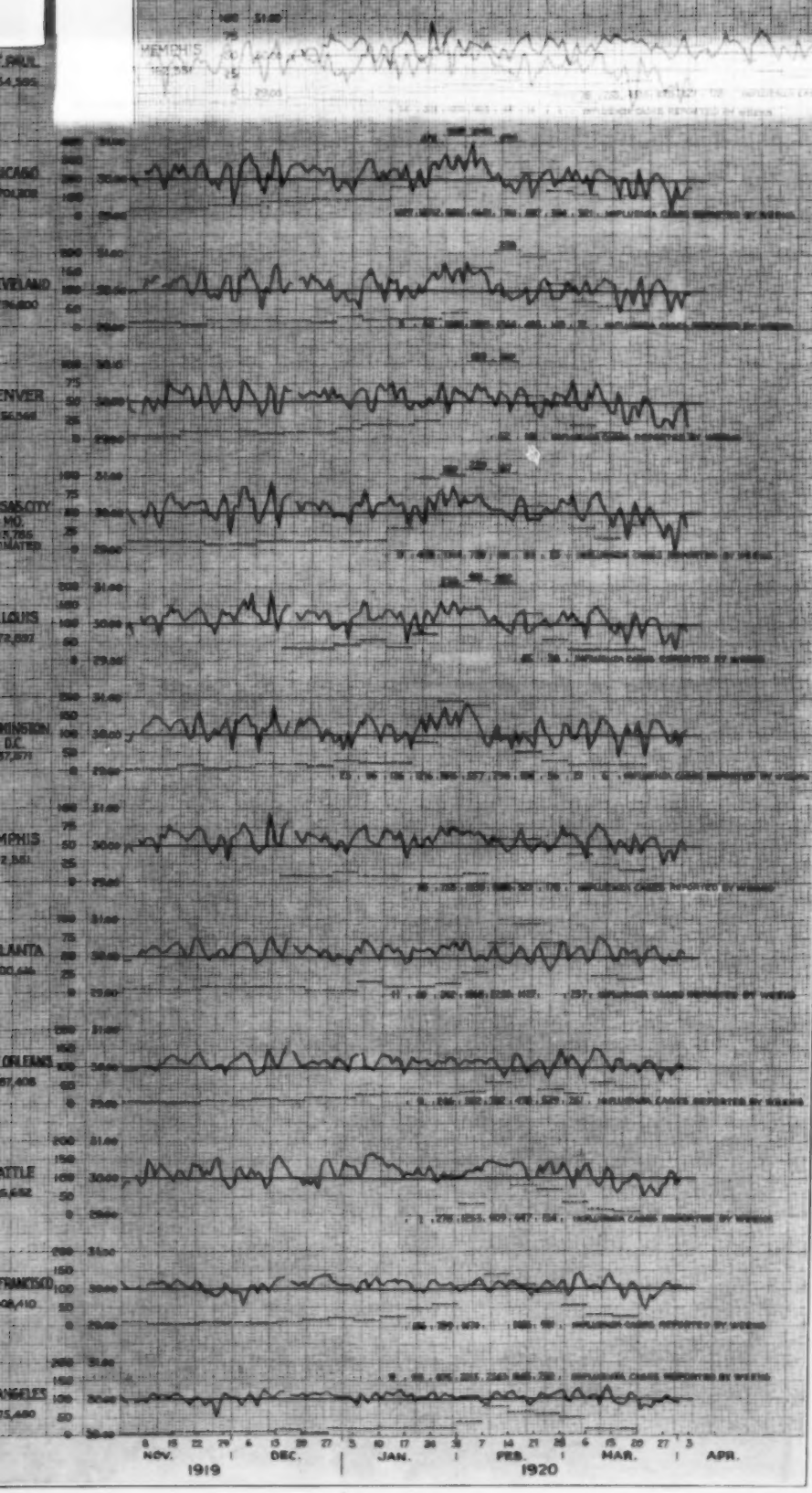

Figure 3

air pressure statistics as being practically free from great errors, but not those giving pneumonia mortality.

The census figures, for instance, differ in some cities materially from those of their health boards. Perhaps a reduction in the mortality line since 1900 is to be attributed somewhat to the policy of the "Census" to eliminate many cases of pneumonia, that had been classified under "primary cause of death." Great errors may also occur by the estimation of population. However, there remains a coincidence of gigantic departures of air pressure and gigantic pandemics. Our largest cities exhibit the same general tendency of rise and fall of both curves during definite periods of many years, and this by means of an annual air pressure curve that necessarily cannot elucidate the relation of cause and effect as a daily air pressure curve. Mean figures may be extremely misleading in certain years. St. Louis and San Francisco have the same mean annual temperature. The extremes of summer and winter in the former city permit of wrong conclusions in this comparison. Similarly low pressure periods at the beginning of 1918 and developing again toward the end of the year reduce the average pressure of the year sufficiently to conceal the unusual anticyclonic activity occurring between the two periods of low pressure. However, the general agreement in rise and fall of the two curves may at once suggest certain possibilities, as a rise of mortality following only certain types of anticyclones. For instance, so-called wandering anticyclones may constitute a positive departure of pressure in some years with a physiologic or pathologic influence on animal life different from that caused by the dynamic anticyclones as they appeared during the different pandemics. Only a careful perusal of daily air pressure conditions as presented on the other charts will give a proper understanding of possible cause and effect. The San Francisco charts are especially illuminating in that respect.

I may add here, that as Hann's [12] figures proved for the period from 1826 to 1885, likewise the evidence given by Richter [1] and Anders [2] corroborates the simultaneous appearance of unusually high barometric pressure during the influenza period from 1889 to 1897. The cities in Europe, generally, show the same years of minimum pressure, 1878, 1885, 1893, 1901-1902, and the same years of maximum as the United States, 1874-1875, 1882, 1889-1890, 1897-1898, 1905-1908. It should be noted here, that Lockyear [14] proved that in certain years the southern hemisphere is affected generally in the same months by high pressure conditions as is the northern.

Figure 2 shows that the different cities (Pacific Coast cities generally included) are exhibiting the same type of Low or High at the

14. Lockyer, N., and Lockyer, W. T. S.: Proc. Roy. Soc. Lond., October, 1902.

same time—with a difference of, perhaps, only one or a few days. This uniformity is remarkable, and is equal to the uniformity found by Hann for Middle Europe. However, the extent of increase and decrease of air pressure in certain Lows and Highs seems extreme in the more northern cities, compared to those in lower latitudes. This is well explained by the record of the variability of the mean monthly pressure in different latitudes, following Hann.[8]

TABLE 1.—MEAN MONTHLY PRESSURES IN DIFFERENT LATITUDES

Latitude, degrees N.	60	56	52	48	46	43	38	32	20
Mean variability, mm.	3.06	2.92	2.58	2.34	1.96	1.80	1.48	1.00	0.40

The air pressure conditions existing before and during the last influenza pandemics in the United States are outlined as follows in the different Monthly Weather Reviews (U. S. Weather Bureau):

August, 1918.—"Pressure was high on several occasions on the West Coast, but there was no progressive movement (two stationary Highs near the 11th and 22nd of August). On the fifteenth rising pressure over northern Manitoba indicated the formation of an independent High." Pressure increased over Michigan, and on the nineteenth "this High was probably the controlling factor of the weather over the northern and central portions of the American continent." There was "a failure of the stationary areas of high pressure to progress eastward."

During *September* "there was entire absence of strong cyclonic action throughout the United States proper" and "the average barometric pressure was above normal through the whole country."

During *October* "the Highs were the dominating weather control of the month—there was more or less merging of North Pacific Highs with Highs which first appeared over the Canadian Northwest. The North Atlantic High was of greater intensity than usual."

During *November* "the Lows during the first half of the month, as in October, were decidedly lacking in intensity—the central portions of the country from the Atlantic to the Pacific were mostly under the influence of high pressure—after the fifteenth there was a marked increase in the intensity of the Lows—practically throughout the month pressure was above the normal off the California coast." Some of the Highs during this month disappeared rapidly. However, on the nineteenth "a marked rise in pressure had overspread Alberta. This rise advanced southward to Montana and to the West Gulf States and a branch of it reached Illinois and Mississippi on the twenty-third." "The Azores High was considerably greater in intensity than usual, and about 1,000 miles northeast of its usual position."

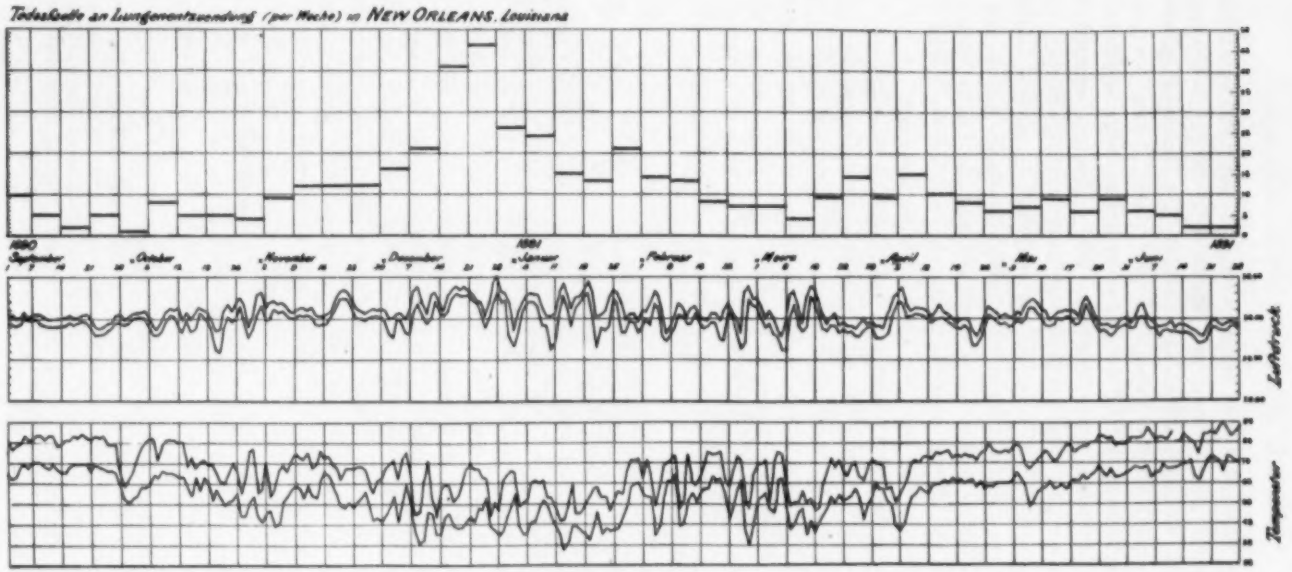
Todesfälle an Lungenentzündung (per Woche) in NEW ORLEANS, Louisiana
1880
September
October
November
December
1881
January
February
March
April
May
June
1882
Luftdruck
Temperatur

Figure 4

During *December* "the average sea level pressure was below the normal in the great central valleys and over the far Southwest, but elsewhere it was generally above normal." The Azores High was still similar to the November type.

During *January*, 1919, "the uniformly low pressure which had prevailed at Honolulu since December, 1917, gradually merged into a type of moderately high pressure and there was still further increase during January, 1919." In the United States "a general increase in pressure over middle latitudes—an almost constantly maintained High over the Plateau region—as a result the average for the month was well above the normal over the entire region from the Rocky Mountains westward, and from the Central plains eastward."

During *February* "pressure in the Northern Hemispheres, as in January, was high over the middle latitude of the continents and the Atlantic Ocean, 30.60 inches over parts of Siberia—a ridge of higher pressure apparently connects the continental Highs of northeastern Asia and the North American continent by way of Alaska and the Bering Sea." For the United States proper we learn that "the average pressure was below normal in practically all portions of the United States."

During *March* "there is a rather pronounced fall over the great continental Highs, amounting to 0.20 inch in Siberia and about half that much on the North American continent."

As the pandemic (Fig. 2) began about Sept. 1, 1918, in Massachusetts,[15] we find that this beginning was preceded by a development of stationary high pressure affecting the West Coast as well as the northeast of the United States during the second half of August.[16] We notice on the chart the entire absence during August and September of strong cyclonic action. The pandemic increased in severity until about October 12 (Boston); October 20 to 26 (New York, Chicago and San Francisco). The pressure likewise increased continuously and during October "the Highs were the dominating weather control." However, after October 5 Boston was experiencing development of Lows, while New York and the other cities had this deficiency in pressure one or two weeks later. The more or less rapid decline of the pandemic runs parallel to this development of low pressure on every city on the chart. About November 20, a second increase of

15. Pub. Health Rep., Sept. 27, 1918, p. 1626.

16. Sept. 17, 1918, report was made of the continued occurrence of a considerable number of cases of influenza at Boston and vicinity, where upward of 200 cases occurred on the day of the report, with a total of about 2,500 cases known to have developed during the outbreak. Sept. 17, 1918, the extensive prevalence of an influenza-like disease was reported at Camp Lee, Va.[17]

17. Pub. Health Rep., Sept. 20, 1918, p. 1604.

pressure begins, and it is followed by a second development of the pandemic in every city relative to this development. The morbidity apparently has its peak about December 20 and the mortality about two or three weeks later. This second increase of air pressure has its peak about December 19, somewhat later in Louisville and the

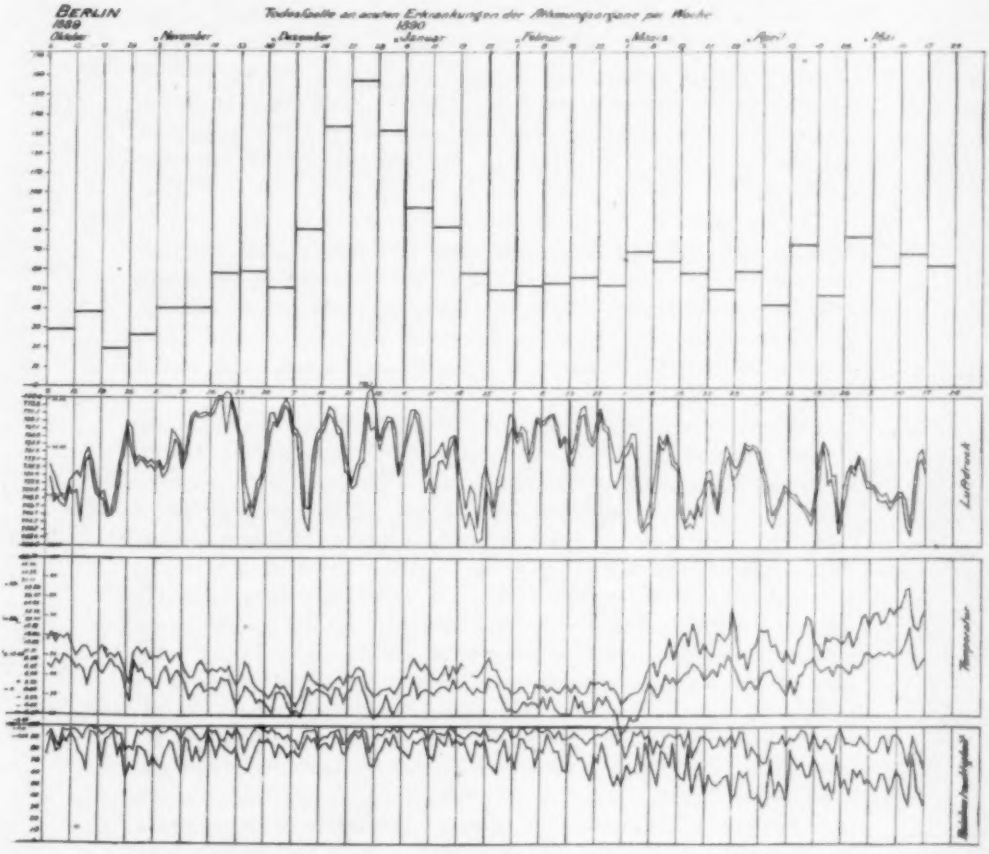

Figure 5

Pacific Coast. Following this, we find a marked intensity of low pressure continuing to February 14 and a few days earlier on the Pacific Coast. A new increase of air pressure during the middle of March is short lived on the Atlantic Coast, but of some duration at Chicago, Cleveland, Kansas City to Louisville, and we find in that area a moderate recrudescence of the epidemic.

No unusual features in weather or mortality develop until toward the end of 1919. In November, 1919, mean pressure in the Northern Hemisphere is characterized by a great continental High over northern Asia, relatively high pressure in a belt which engirdles the globe about 35 degrees north latitude." The weather in North America is largely controlled by the depth and persistence of the low pressure in the North Pacific—also by cyclones which form on the southern border of the semi-permanent High in middle latitudes—but cyclonic systems of pronounced character were notably absent. The average pressure showed the highest area extending as usual from the South Atlantic States northwestward to the northeast Rocky Mountains and Plateau regions with the maximum over Wyoming. Pressure was lowest over the Southwest."

During December, "the pressure at the Azores was considerably higher than usual." In the United states "the weather was distinctly under anticyclonic control, but during the third decade of the month lower pressure was the rule in practically all parts of the country. The excess of average pressure of December was least over the South Atlantic and East Gulf States and along the central and south Pacific Coast."

During January, 1920, "pressure over the United States alternated between low and high during the first and second decades, except in the Rocky Mountain Region, where it was high, while during the last decade it was almost continuously above normal throughout the entire country. Fifteen anticyclones entered the United States against nine, the average number for January—ten of them the Alberta type and four Plateau and Rocky Mountain region type. The most important features were the persistence of high pressure from the seventh to the nineteenth over the northern and central plateau regions—high pressure prevailed over the northern districts rising above 31 inches in eastern Montana. This high area moved along the northern border, but its influence was felt far to the southward. At the end of the month this high pressure area covered the northeastern States and some of the highest barometer readings ever observed in that region were reported. The average pressures for January were above normal in all portions of the United States and likewise in Canada as far north as observations disclose."

February opened "with a pronounced fall of pressure near the Aleutian Islands, where since January 10 it had been abnormally high. The extremely high area of the end of January moved rapidly into the Atlantic and was quickly followed by another that prevailed for several days from the Great Lakes eastward. During the same period pressure was generally high over the far West and low in the Southeast, where

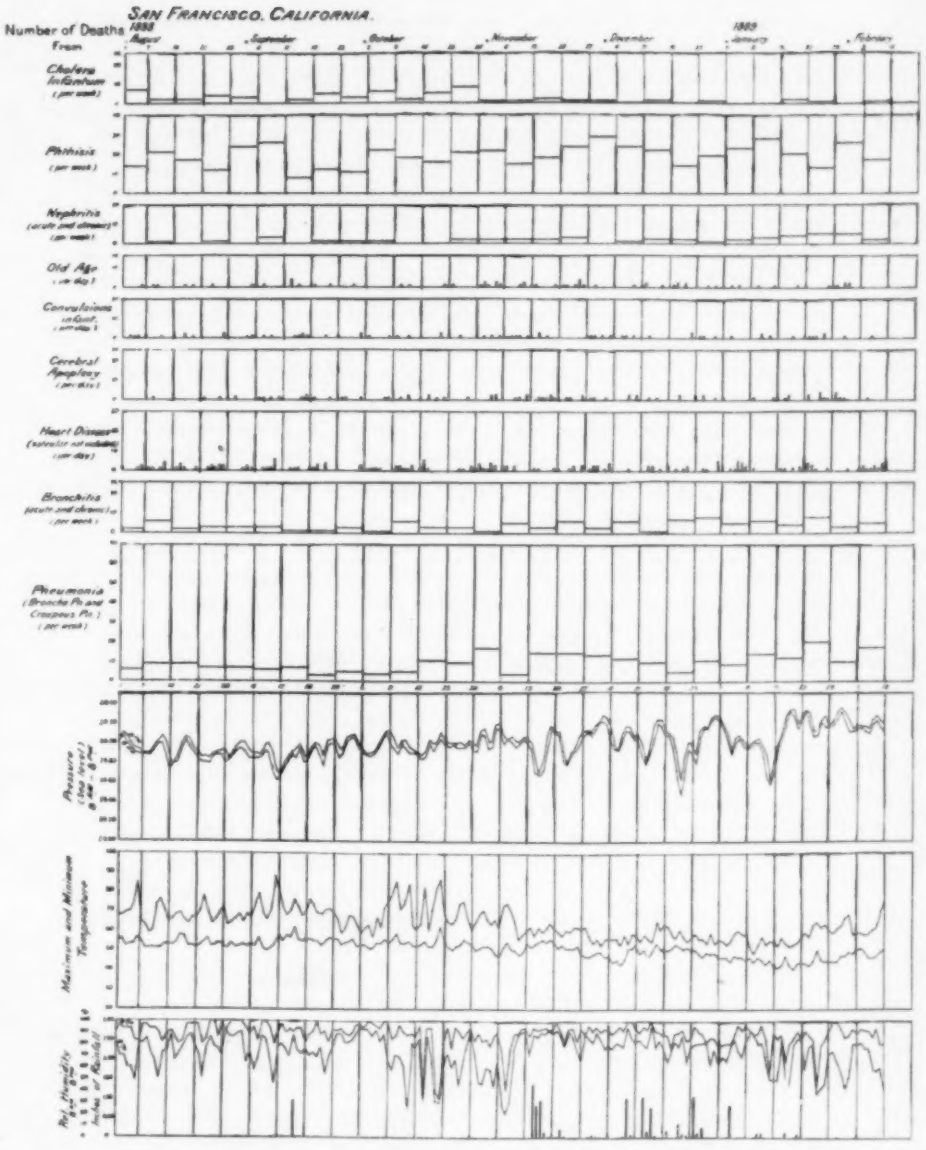
SAN FRANCISCO, CALIFORNIA.
Number of Deaths From
1898
August
September
October
November
December
1899
January
February
Cholera Infantum
Phthisis
Nephritis
Old Age
Convulsions
Cerebral Apoplexy
Heart Disease
Bronchitis
Pneumonia
Pressure
Maximum and Minimum Temperature

Figure 6

a Low moved northward from Florida up to New England. The average pressure of February was above normal over practically all the portions of the United States and Canada from the Mississippi and the Great Lakes westward to the Pacific, the departure increasing in the far northwestern districts, where at points it was the highest on record. In the eastern districts of the United States, as well as of Canada, it averaged considerably less than normal, particularly along the middle Atlantic Coast." Twenty cyclones entered the United States as against 11.9, the normal number, and ten anticyclones as against 7.8 normal.

March "was characterized by a remarkable series of cyclones that moved across the United States. Abnormally low pressures prevailed in every instance. An extensive and marked high pressure wave followed the storm of March 1 to 7, principally in the Southeastern States, but there were no other Highs of consequence—the averages of the month were below normal over practically all portions of the United States west of the Mississippi, north of the Ohio and over Canada." Eighteen cyclones entered against 11.8 normal, and ten anticyclones against 8.5 normal.

A general tendency to increase of pressure over the North American continent and a relative absence of cyclonic activity again characterize the weather of two months preceding the January, 1920 pandemic (Fig. 3). But instead of the gradual increase of high pressure we find, near the end of 1919, a more explosive increase of high pressure and during January, 1920, a gigantic High controlling the weather of the continent during the four or five weeks of the pandemic. The pressure condition during November and December, 1919, apparently helped to prepare the way, as we find a distinct gradual increase in the pneumonia mortality, beginning after the middle of November, notably in New York and Chicago. At the beginning of December, this influence is shared by almost all the cities on the chart, while the actual beginning of the pandemic, as indicated by the morbidity figures reported by weeks, may be traced directly to the relative development of very high pressure beginning about January 3 in the different cities.

A careful study of the individual cases in regard to the relative value of intensity of pressure and the partial interference by minor cyclonic action easily emphasizes the parallelism of the pandemic and the high pressure condition, which latter comes to an end about February 4 by a most intense cyclonic action. From the first week in January we note a very uniform pressure type for the cities on the Atlantic Coast and for the area from St. Paul and Denver to Chicago, Kansas City, Memphis and Atlanta. New Orleans participates in a general way, but the Pacific Coast again resembles the Eastern type,

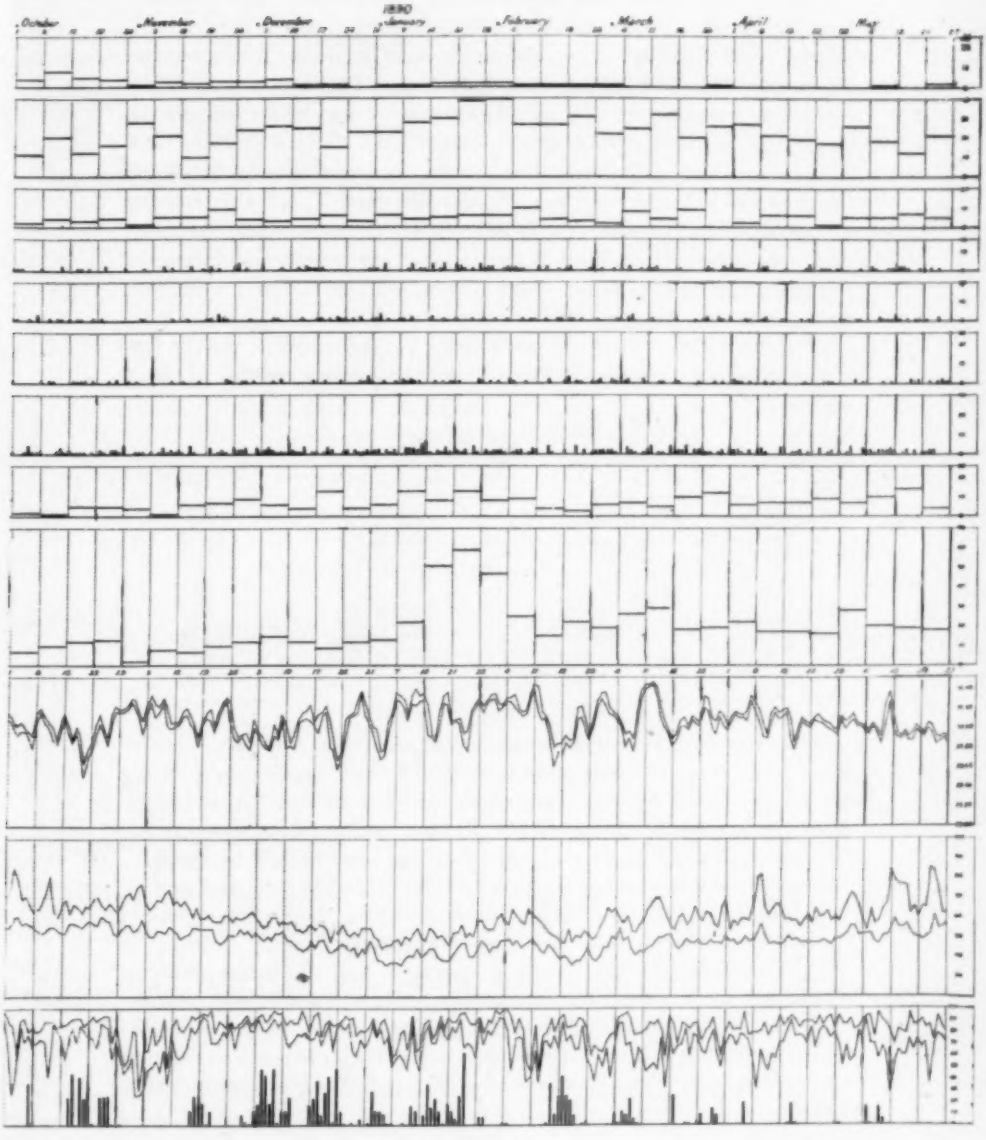
1890
October
November
December
January
February
March
April
May

Figure 7

which antedates the Pacific type by from one to two weeks. The Chicago type is at least one day ahead of the Atlantic Coast type and here, if we consider the report of influenza cases, is the first firm hold on the population—the other cities following in direct proportion to the development of the High over their area. The largest number of cases were reported for two weeks previous to the sudden collapse of the High, which occurred after February 4. Only Baltimore and Atlanta have a higher figure of cases for the week ending February 19, and San Francisco and Los Angeles likewise. Local difference in air pressure runs parallel to this difference. It is clear that the mortality line would lag behind from one to three weeks and longer.

Morbidity statistics relative to influenza are still far from ideal, but were, during the January, 1920 pandemic, probably more accurate than ever before. They were not sufficiently available before, except for a few states and cities.[18] Of these we find the highest number of cases reported:

TABLE 2.—Influenza Morbidity Statistics

	For Week Ending	Cases
Maine	Oct. 26, 1918	6,754
Vermont	Oct. 21, 1918	6,949
New York City	Oct. 19, 1918	22,884
New Jersey	Oct. 19, 1918	77,215
Chicago	Oct. 19, 1918	12,183
Minnesota	Oct. 26, 1918	26,853
St. Louis	Oct. 19, 1918	4,043
Kansas	Oct. 19, 1918	14,892
Washington, D. C.	Oct. 12, 1918	9,708
Atlanta	Oct. 19, 1918	1,594
New Orleans	Oct. 19, 1918	17,070
Arizona	Oct. 19, 1918	3,530
San Francisco	Oct. 26, 1918	8,682

The report giving these figures states that "they are not exact or even more than approximately accurate." Only in Baltimore[19] has the attempt been made to trace cases of influenza back to August 1, 1918, but none are tabulated for August, while from September 1 an ever increasing number of cases is given until middle of October. A rather rapid decline begins about October 21. The outstanding fact is again the collapse of the epidemic following closely the cyclonic action, which begins with the second decade of October, 1918.

Even during the last pandemic mortality and morbidity statistics have been rather crude, but sufficiently complete in some cities to compare the time factor of the outbreak, peak and decline of the pandemic to the numerical values of atmospheric conditions, as measured by air pressure figures. The two factors easily explain the variation among cities in their different epidemiologic characters. Especially the Jan-

18. Pub. Health Health Rep., Nov. 8, 1918, p. 1914.
19. Pub. Health Rep., March 14, 1919.

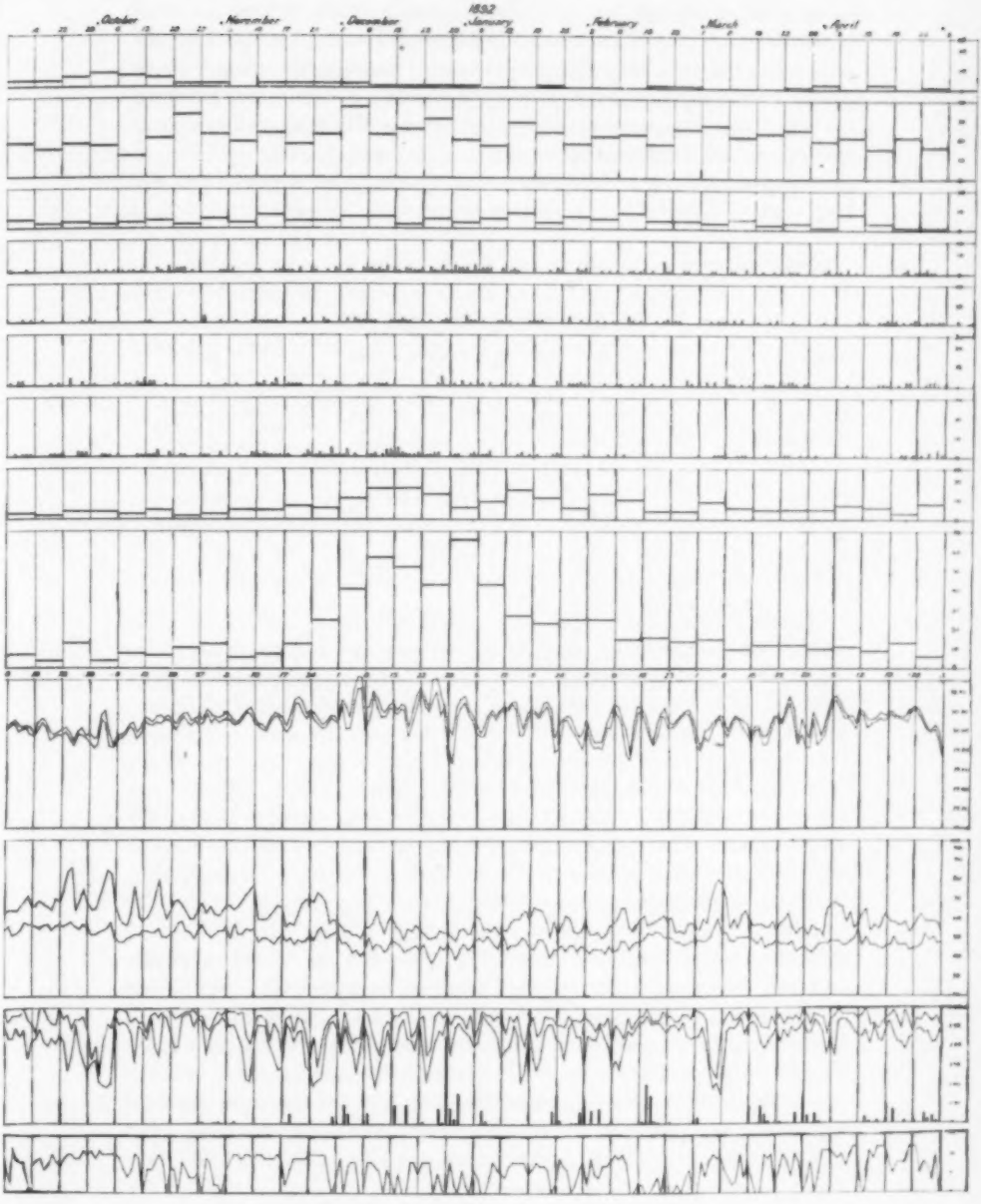
October
November
December
1892
January
February
March
April

Figure 8

uary, 1920, pandemic proves the indisputable truth of their interdependence. Looking back to the 1890 pandemic we recognize in the examples of Berlin, New Orleans and San Francisco, the same decisive characteristics. They exhibit the same increase of air pressure toward the beginning, the same extreme High during the peak and the same collapse of the pandemic by the start of intense cyclonic action.

Comparing the San Francisco, New Orleans and Berlin charts for the pandemic 1889-1891, we find the following (Figs. 1, 2, 3, 4, 5):

TABLE 3.—Influenza Morbidity, Air Pressure and Cyclonic Action

	Mortality Peak or Increase	Air Pressure Peak or Increase	Cyclonic Action
Berlin	Dec. 21-28, 1889	Dec. 9-23, 1889	Dec. 23-30
Second wave	Dec. 30, 1889 to Jan. 17, 1890 and Feb. 1 to March 8, 1890	Dec. 25 to Jan. 17 and Feb. 1-22, 1890	Jan. 18-31 and Feb. 23 and following
San Francisco	Jan. 21-28, 1890	Jan. 7-21, 1890	Jan. 21-28
Second wave	Feb. 18 to March 18	Jan. 28 to Feb. 11, 1890	Feb. 11 to March 11
New Orleans	Dec. 14-28, 1890	Nov. 1 to Dec. 28, 1890	Dec. 29 to Jan. 11, 1891
Second wave	Jan. 28 to Feb. 1, 1891	Jan. 4-20, 1891	Jan. 20 and following
San Francisco	Dec. 8 to Jan. 5, 1891	Nov. 20 to Dec. 6, 1890	Dec. 27 and following

If we review the air pressure conditions during the recent pandemics, we recognize the identical anticyclonic action that characterizes the 1889 to 1891 pandemics. The first advent of those pandemics is heralded by a protracted continuous anticyclonic development, not interrupted by any cyclonic action. The first big pressure wave is followed then, as now, by one or two succeeding Highs, lasting again for weeks at a time. The intervals between them have cyclonic action. The mortality line has the same relation to the pressure types in both series of pandemics. Somewhat different is the pressure type at the time of the 1890-1891 pandemic at San Francisco, and of the January, 1920 pandemic in the United States. Both these types are not followed by succeeding waves. Both types have a more abrupt rise and fall of mortality and air pressure lines. The 1890 and the recent pandemic occurred during an advent of high pressure over our hemisphere, that in each case had been extending over some years previous to the outbreak of influenza and that apparently came to its highest and more specific development during or just ahead of the pandemic. I have charts that give the weekly mortality and daily air pressure for San Francisco from 1888 to 1904 (16 years) and for Berlin from 1887 to 1911 (24 years). The explosive appearance of influenza and pneumonia mortality are there confined exclusively to such periods as are marked by the advent of unusual anticyclonic action.

In addition to these facts we may consider the time relation of influenza pandemics and high pressure periods for middle Europe (since 1827) and for the United States (since 1873).

Of course, this secular coincidence of the pandemics and the high pressure periods does not enlighten us about the cause of an influenza pandemic or of an increase of pneumonia mortality, but it opens a window into the strange character of influenza. It certainly points to a distinct interdependence of the two, and points to the anticyclone as the decisive factor.

TABLE 4.—TIME RELATION OF INFLUENZA PANDEMICS AND HIGH PRESSURE PERIODS

Air Pressure Periods	Influenza and Pneumonia Pandemics
High 1801 to 1841, including "highest air pressure period (1832 to 1836) not equaled during the period 1826 to 1885." [18]	"Exceedingly intensive and extensive influenza period over the entire globe and consisting of the pandemics 1830 to 1832, 1833, 1836 to 1837." [20]
Low 1842 to 1847, beginning in some countries 1838.	No pandemics, but minor epidemics
High 1847 to 1851	Influenza pandemic 1846 to 1848, 1850 to 1851.
Low 1851 to 1855, distinctly low from Warsaw to Palermo	No pandemics.
High 1856 to 1864.	Minor epidemics 1855, 1857 to 1858. Irregular outbreaks 1860 to 1870.
Low 1874 to 1878, distinctly low pressure over United States and Europe.	Definite lowering of pneumonia mortality 1875 to 1878 over United States. Minor local epidemics 1873 to 1875, and 1879.
High and increasing 1881 to 1900 over the United States and Europe and continuing.	Local epidemics, principally in Russia, 1885 to 1888, also affecting the United States. Influenza pandemics 1889 to 1891 and irregular outbreaks to 1900
Low 1896 to 1902.	No epidemic of note.
High 1902 to 1930, definite period of increasing high pressure.	Pneumonia epidemics 1906, 1907, 1910, increasing incidence after 1915. Influenza pandemic 1918 to 1920, probably unequaled in severity.

The very source of the pandemics is found to be in that part of inner Asia or North America on the northern hemisphere where the centers of highest pressure are located on those parts of the continents. The air, carried by such dynamic anticyclones during their extreme development all over the two continents, is distributed with an anticyclonic velocity equal to that of our railroad trains.

The direction in which the air is carried out of the center of an anticyclone, varies, of course, with the location of the center. Suppose the center be at St. Louis, the air flowing out of the center would be carried by northwesterly winds toward Boston, by northerly winds to the middle Atlantic Coast, by northeasterly winds to the Gulf States, by easterly winds toward New Orleans and Texas, by southeasterly winds toward the Pacific Coast. Hann [3] summarizes thus: "The air circulation in the dynamic barometer maxima of the United

20. Leichtenstern, O., and Sticker, G.: Influenza, Ed. 2, Wien. and Leipzig, 1912.

States, therefore, consists (1) of a true downward directed gyration near its center and extending about 500 kilometers outward; (2) in its outer circumference the motion everywhere has an outward direction and represents a forced rotating motion similar to a whirl in a stream." It is also stated by him that the barometer minima do not supply the air that enters the maxima above, as they do not reach to such height. The distance of the center of a dynamic anticyclone from that of a cyclone is generally about 2,000 miles in the United States and often more than that in Europe.

It is clear that only a most careful study of the daily weather maps will explain the actual air conditions in a certain district relative to a dominating influence of a High or Low. Furthermore, only such study will inform us whether a High is of the quickly wandering type or of a stationary dynamic character. Only continuous crowding of air over vast parts of the country, for instance, over the entire United States or over Europe, lasting quite a number of weeks, seems to carry the character that increases pneumonia mortality severely and paves the way for or starts a pandemic. As we have no special sense for electricity, nor for air pressure and its variations, we do not become aware of the differences that exist in the air we breathe during changes in those factors. It seems reasonable to consider the possibilty that during the development of such unusual high pressure conditions, the physicochemical nature of the atmosphere that reaches our lungs has been altered in such a way that it may affect us more or less disastrously. Or, we may be induced to suppose that such air has become the carrier of a virus. The air of an anticyclone has been descending from a 10 to 20 kilometers height and naturally has been differently qualified during different solar activity. As soon as low pressure sets in, which carries the anticyclonic air away from us, influenza and pneumonia decline. It is difficult to harmonize this behavior with a bacteriologic origin of those diseases.

If we assume that the atmosphere acts as carrier of the cause of influenza, we are facing similar difficulties, as when we were forced by certain facts to assume that the water acted as carrier of the cause of typhoid fever and cholera. Now we know that infection of water is the most common source of widespread epidemics, originating in the contamination of a well or spring. Such epidemics are often as "explosive" as the pandemics. But how can infection be carried by the air, except with dust? But why do we insist on a virus, on an infection as the cause? Certainly only for sake of an analogy, that at best can be only a partial similarity. There is, however, a greater similarity between the march of the pandemic and that of the dynamic anticyclone. Both reach ships on the ocean, islands, distant camps that had

been as far removed from the pale of civilization as the North Pole. Is there, perhaps, a special physicochemical quality imparted to the air we breathe during a pandemic, imparted, for instance, by the radiant energy of the sun, by radioactivity, by ozonization? Lenard and Ramsauer [21] define the principal effect of the solar output on the atmosphere: First, the development of ozone "welche ziemlich tief herabreicht, weil sie schon durch schwach absorbierbare Strahlen bewirkt wird." Second, the continuous creation of fognuclei in the upper atmosphere. ("Amonnitrat und Nitrit aus dem lichterzeugten Ozon und dem Ammoniak der Luft, wahrscheinlich auch Wasserstoffsuperoxyd aus Wasserdampf.") Third, continuous creation of carriers of electricity.

W. J. Humphreys [22] says: "One would expect to find an appreciable amount of ozone in the upper atmosphere, but, owing to its unstable nature and its great power of oxidation, very little near the earth. Only traces of ozone are found in the lower portions of the air and when there is much moisture and the temperature is high the amount is vanishingly small. On the other hand, Augstrom, by examining the absorption bands in the solar spectrum, has detected the presence of a very considerable amount of ozone, which must be in the upper air." "Ozone is produced by the action of ultraviolet radiation on cold dry oxygen; its amount, therefore, must vary with the amount of ultraviolet radiation sent out by the sun and this is a variable quantity." "Besides ozone is abundantly produced by the action of silent electric discharges; therefore, the amount of ozone in the atmosphere, since it results from the action both of auroral discharges and of ultraviolet radiation, will vary with their increase and decrease. The increase we should expect in the higher latitudes, where the auroral discharges occur. The equator to pole circulation of the upper atmosphere, and the paralleling of magnetic lines of force by auroral discharges, might very well lead to a greater amount of ozone in the upper air of temperate and polar regions than in that of the tropics."

The amount of ozone found in the air we breathe has repeatedly been estimated to amount to more than 1 part in 700,000 parts air. The effect of ozone on the respiratory organs has again lately been investigated. Jordan and Carlson [23] summarize the results of their research work, in part, as follows: "Human beings are injuriously affected by amounts of ozone far less than are necessary to produce bactericidal effect, and there is no evidence for supposing that a quantity

21. Lenard, P., and Ramsauer, C.: Sitzungsberichte der Heidelberger Academie der Wissenschaften, Abh. 24, 1911, p. 42.

22. Humphreys, W. J.: Astrophysical J. **32**: No. 2.

23. Jordan, E. O., and Carlson, A. J.: Ozone. J. A. M. A. **61**:1007 (Sept. 27) 1913.

of ozone than can be tolerated by man, has the least germicidal action. In concentrations that appreciably affect man, ozone appears to have uniformly an injurious action. This action is primarily on the respiratory passages—irritation of the sensory nerve endings, and irritation, corrosion and depression of the epithelial cells. The depression and drowsiness produced by ozone are due to the intense irritation of sensory nerve endings (vasomotor effect) in the respiratory tract, as well as to the secondary effects of the change in the activity of the aveolar epithelium. Nor can we accept the suggestion of Hill and Flack, that small amounts of ozone may be of therapeutic value in certain diseases of the respiratory tract by reason of the hyperemia following the ozone irritation. The ozone irritation leads to intense hyperemia of the respiratory tract, . . . The cells injured by ozone are probably more readily invaded by bacteria and have less than normal power of healing despite the hyperemia. The physiology of ozone points to the conclusion that the use of this poisonous gas as a therapeutic agent is either valueless or injurious." As these authors say: "The cardiac and vasomotor changes on exposure to ozone have not been extensively studied." "Here we have as an effect of exposure to ozone, generally considered harmless, symptoms as headache, sore throat, pain in the chest, intense irritation of the respiratory tract, and even if prolonged exposure to ozone should prove harmless to the robust person, what about the unfortunate person whose lungs have only slight power of resistance? Concentrations of ozone of 1 part per million parts of air are certainly injurious, but it does not follow that the weaker concentrations of ozone are proportionately injurious."

In addition to this research work we should consider the "studies of the respiratory inflammatory processes initiated by the inhalation of toxic gases" (used in modern warfare) made by Winternitz, Wason and McNamara.[24] They state that "the pathology produced by the inhalation of these poisonous vapors is analogous to that found in influenzal pneumonia." Their conclusions contain the following: "A basis for the interpretation of the respiratory lesions of influenza is offered by the analogous changes in the respiratory tract initiated by the inhalation of poisonous gases. The respiratory lesions are dependent primarily on the damage produced by the true etiologic agent and the systemic capacity to compensate, and only secondarily on invasion by the bacterial flora of the mouth and inspired air."

These findings gain in importance by the general agreement of clinicians that the influenza infection is carried directly into the respiratory tract. D. Symmers[25] concludes thus; "From the opportunity

24. Winternitz, Wason and McNamara: The Pathology of Influenza, Yale University Press, 1920.

25. Symmers, D.: J. A. M. A. **71**:1482 (Nov. 2) 1918.

that I have had to observe at necropsy and in the living patient, it appears to me to be probable that the prevailing pandemic of influenza is attended by pneumonic lesions from the beginning. Moreover, the distribution of the pathologic changes in the lungs is such as to suggest that the infection is introduced by way of the respiratory tract. . . . In those cases in which death has occurred twenty-four or thirty-six hours after the development of detectable pneumonic signs, it is scarcely conceivable that the massive solidification of the lungs could have taken place with corresponding rapidity. The suggestion naturally follows, that every case of pandemic influenza should be regarded from the outset as pneumonic."

Park [26] writes: "Epidemic influenza is a disease primarily attacking the respiratory tract." Conner [27] writes: "In the present epidemic there has been, for all practical purposes, only a single type—the respiratory." Kinsella [28] says: "Whatever the cause of the disease may be, it is clear that this agent is one to which the body is not accustomed." McLaughlin [29] concludes: "These indications suggest—either that in the great pandemic we were dealing with a new and entirely different disease, or that the immunity conferred by an attack, if any, was of a very fleeting character." Of course we could not acquire immunity from exposure to an irritating gas similar to ozone. The great clinician Ziemssen wrote many years ago, alluding to epidemics of influenza: "After all we cannot but assume that there must be general conditions, which appear and disappear simultaneously in great expanse of space. Of what nature these influences may be is perfectly dark. We would not be forced to think of miasm or contagion. We are more led to believe that fluctuations of other conditions, extending over great areas of the surface of our globe at the same time furnish an analogy."

CONCLUSIONS

In conclusion we should consider the following facts:

1. The assumption, that the propagation of influenza is analogous to that of an infectious disease, has so far no foundation in fact. We have no proof that influenza is caused by bacterial infection. The cause of influenza is still unknown. We have not succeeded in inoculating influenza from person to person; we cannot transmit it experimentally. A "drop infection" from person to person has likewise not been proved. Frost [30] believes in "contact in the broad sense" and

26. Park, W. H.: J. A. M. A. **73**:318 (Aug. 2) 1919.
27. Conner, L. A.: J. A. M. A. **73**:321 (Aug. 2) 1919.
28. Kinsella, R. A.: J. A. M. A. **72**:717 (March 8) 1919.
29. McLaughlin, A. T.: The Shattuck Lecture, Boston M. & S. J., July 1, 1920.
30. Frost, W. H.: J. A. M. A. **73**:313 (Aug. 2) 1919.

adds: "As regards preventive measures, the efficacy of those carried out—is not proved." Howard and Love [31] state that, "in U. S. Army Camps, where all accepted measures for the prevention of the spread of respiratory disease (during the pandemic) were vigorously enforced, the incidence of the disease apparently was as great as in other camps where such measures were less rigidly and effectively applied." Transmission of influenza is more logically explained by an air which may carry in infective virus or a poisonous gas, an animate or an inanimate agent, into our lungs and which naturally has free access everywhere. We cannot guard ourselves against such air, except by masks, which would nullify the bad effect of such air. The research work describing the effect of inhalation of ozone and warfare gas proves that the pathology of influenza can readily be explained by the assumption that a poisonous gas is the cause of the pandemic.

2. Atmospheric conditions that are characteristic, we could as well say pathognomonic, for influenza and its spread are well defined. The cycles in which the pandemics alternate with periods of relative quiescence are distinctly covered by the cycles of high air pressure periods during and before the pandemics and of low air pressure periods following them.

3. The first appearance of influenza cases in a pandemic, and the full development of the latter, are geographically in direct relation to the appearance and development of certain anticyclonic conditions. The successive seizure of great districts of the continent invariably originates in one or the other center of great anticyclonic action on the globe, as in inner Asia, Bokhara, and in Canada during the 1890 pandemic, and as in the region of the "Canary Island High" (Spanish influenza), and in Canada during the 1918 pandemic.

4. The influenza pandemic extends, spreads in the same direction and with the same velocity as the great anticyclone spreads from its center over a continent. In the United States therefore, it generally attacks first those districts that lie in the path of the Alberta type or the Hudson Bay type.

5. The prepandemic weather, as the charts prove, remains for a long period free from any cyclonic action. It is the forerunner of the coming avalanche of atmosphere.

6. Increases of influenza morbidity preceding a great pandemic are always in harmony with similar increases of an anticyclonic type of weather.

7. As the period of very high pressure of from 1830 to 1840 was synchronous with the greatest pandemic before our times, similarly, the 1890 and 1918 pandemics were heralded by an ever increasing . air

31. Howard and Love: Influenza, Mil. Surg. **46**:522 (May) 1920.

pressure since 1878, reaching the highest figures only during the period of the last pandemic, as the Bismarck pressure line so well illustrates in Figure 1.

8. The anticyclonic weather conditions for some weeks before and during the prevalence of a pandemic are almost stereotyped for every city on the charts. The usual type for the United States is the Alberta type. The gigantic masses of air that it whirls and spreads over the country in a southerly and easterly direction with the velocity of a fast train, are represented by the more or less extreme positive departures of the air pressure from normal in the most typical manner in every city. Distinct cyclonic action is, then, missing in every single instance, and the only type in evidence is prolonged high pressure for a longer period, as in September and October, 1918, or for a shorter period of highest air pressure, as in January, 1920.

9. Likewise, we find in a stereotypic fashion the beginning of a decrease of morbidity in every city following the first well marked cyclonic action. As the anticyclonic period is common to the entire United States, proportionate only to the time necessary for the spread of its masses of air, likewise, the cyclonic action, when it arrives, puts its stamp on every city almost on the same day.

10. Extraordinary proof of the interdependence of the pandemic and an extreme high pressure period occurs in January, 1920. The beginning of both is clearly defined and the decrease of morbidity appears in direct relation to cyclonic action, beginning in the first week of February.

11. This interdependence gains additional value by the research work on prolonged exposure to ozone and other poisonous gases and the injury to the respiratory tract caused thereby. In fact, it is clear that the symptoms caused by inhalation of such poisonous gases resemble the influenza symptoms perfectly.

12. We have reason to assume that air of some anticyclones contains ozone in unusual quantity as a product of unusual solar output. If we hesitate to deduce that ozone is causative of influenza because its odor and the gas itself has not been detected in the air we breathe during a pandemic, we must admit that no attempt has been made to find it.

Of course some degree of speculation cannot be avoided if we seek for any theory to guide us in the labyrinth of influenza. The possibility of its spread by the atmosphere is consistent with the facts. It has the merit that it leads us to an experimental study of the air, and it gives us ozone as a guide. A second Schoenbein may arise and find a chemical body, similar to ozone, or we may extend Haldane's research work, which suggested that the rate of supply of oxygen to

the tissues by the blood in the systemic capillaries in the lungs is insufficient in influenza for the normal processes of life.

We cannot, after the presentation of the foregoing facts, escape our duty to demand a critical analysis of the air during the different air pressure conditions and especially during the epidemics of the respiratory organs. Furthermore, we have achieved the very important practical gain that we may predict an increase in pneumonia morbidity whenever an extensive anticyclone is approaching any territory in question, and we have a warning of a coming explosiveness of morbidity in general whenever the magnitude of the approaching anticyclone warrants it. The necessary information, easily given by the Weather Bureau, would make a suitable preparedness possible to meet the emergency. A failure to recognize this fact would seem to involve a great responsibility.

Spirochetal Pulmonary Gangrene

Drs. Fishberg and Kline, authors of the paper with the above title, published in the Archives of Internal Medicine, January 15, 1921, p. 61, request the addition of the following paragraph to their paper:

The occurrence of fusiform bacilli and spirochetes, not only in the exudate over the gums but also in the gangrenous lung tissue, lends support to the belief that this is a case of aspiration pneumonia followed by pulmonary gangrene in which innumerable mouth organisms, Vincent's spirochetes and fusiform bacilli from the gingivitis were aspirated into the lungs, the mouth organisms producing the widespread consolidation and the spirochetes the associated gangrene.